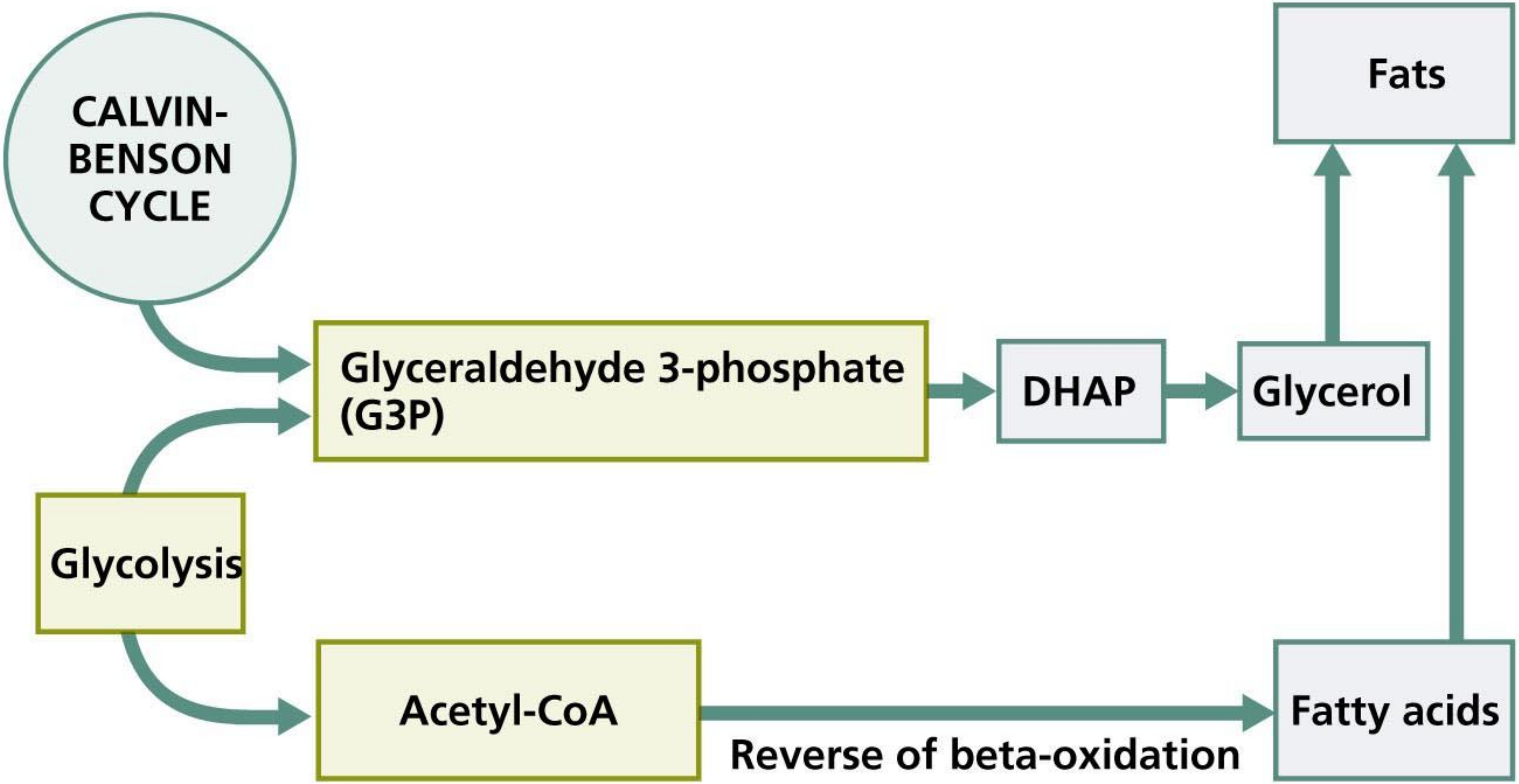
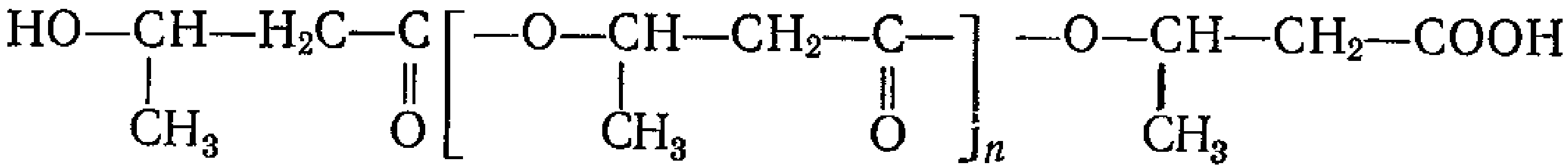
Синтез липидов

- Омыляемые (ЖК и их производные, в т.ч. глицеро- и сфинголипиды, эйкозаноиды)
- Неомыляемые (изопреноиды, в т.ч. стероиды, терпены, токоферолы, каротиноиды)

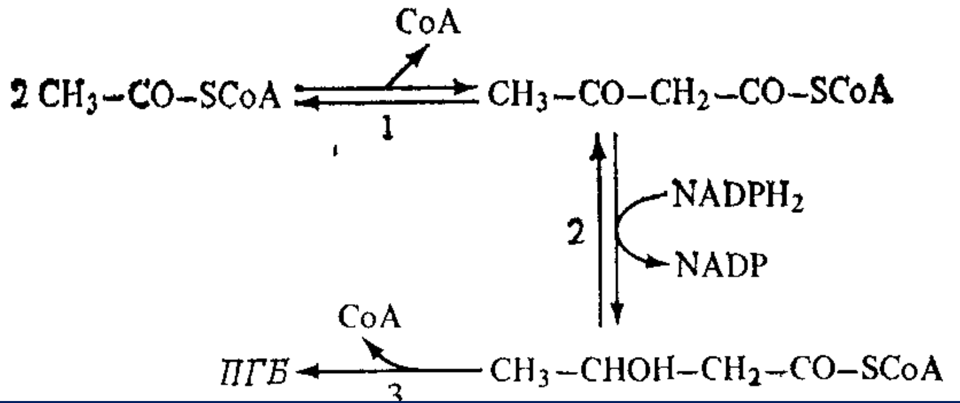
Anabolic Pathways – Lipid Biosynthesis





$$HO-\underset{CH_3}{\underset{|}{CH}}-H_2C-\underset{O}{\underset{\|}{C}}\left[-O-\underset{CH_3}{\underset{|}{CH}}-CH_2-\underset{O}{\underset{\|}{C}}-\right]_n-O-\underset{CH_3}{\underset{|}{CH}}-CH_2-COOH$$

Поли-β-гидроксибутират

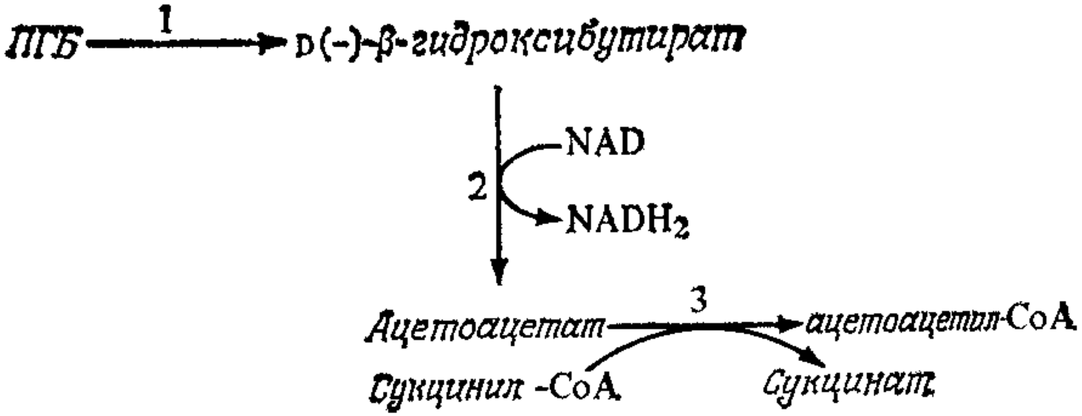


Синтез полигидроксибутирата у *Azotobacter*

1 — β-кетотиолаза,
2— D(—)-β-гидроксибутирил-CoA—ДГ,
3—D(—)-β-гидроксибутирил-CoA — полимераза.

Расщепление ПГБ:

1− деполимераза,
2− ГБ-ДГ,
3− КоА-трансфераза



Biosynthesis of fatty acids

ACP = acyl carrier protein
hold growing fatty acids

Fatty acids are synthesized
2 carbon at a time

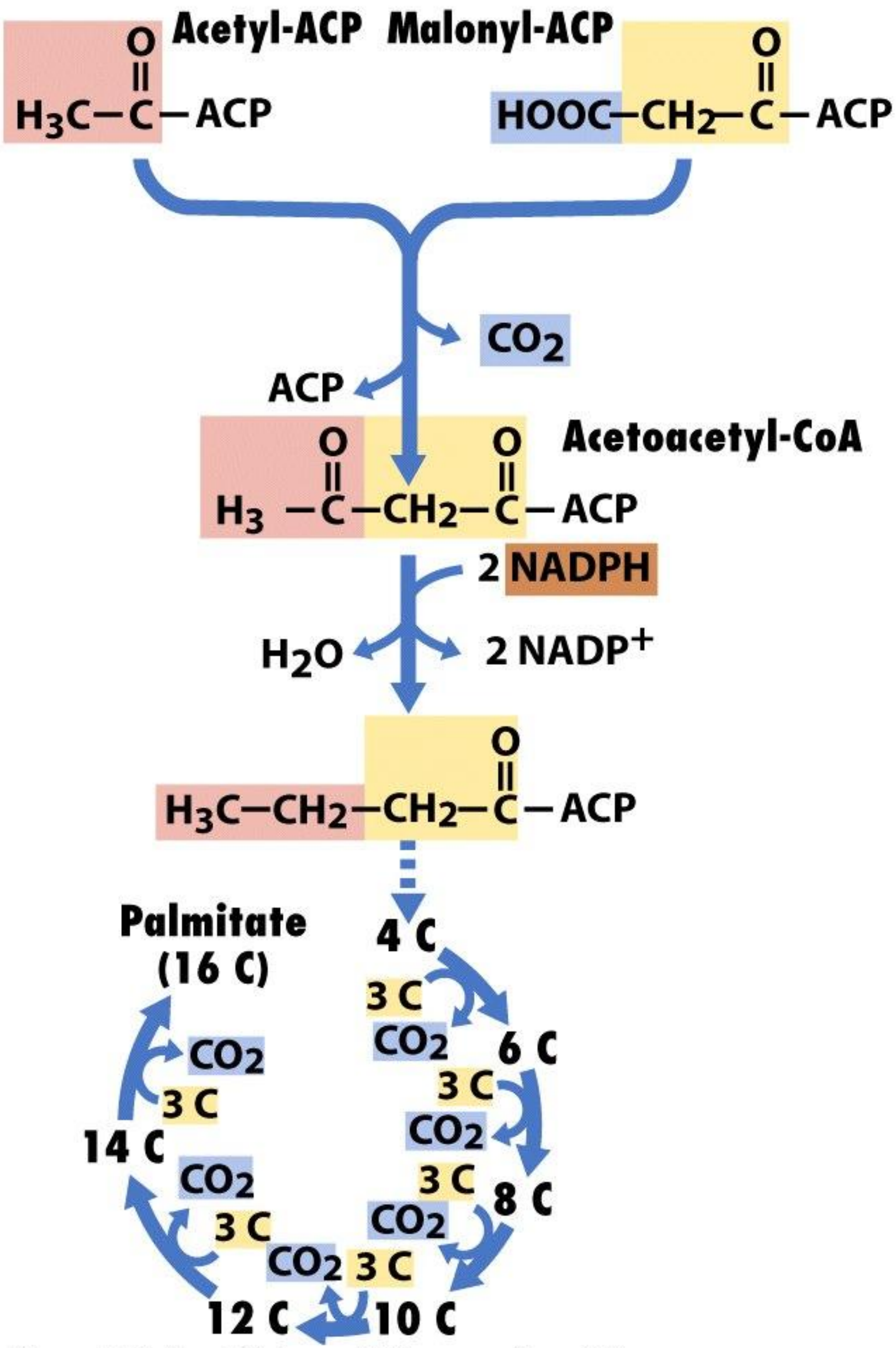


Figure 5-29 Brock Biology of Microorganisms 11/e

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Overview of Fatty Acid Synthesis

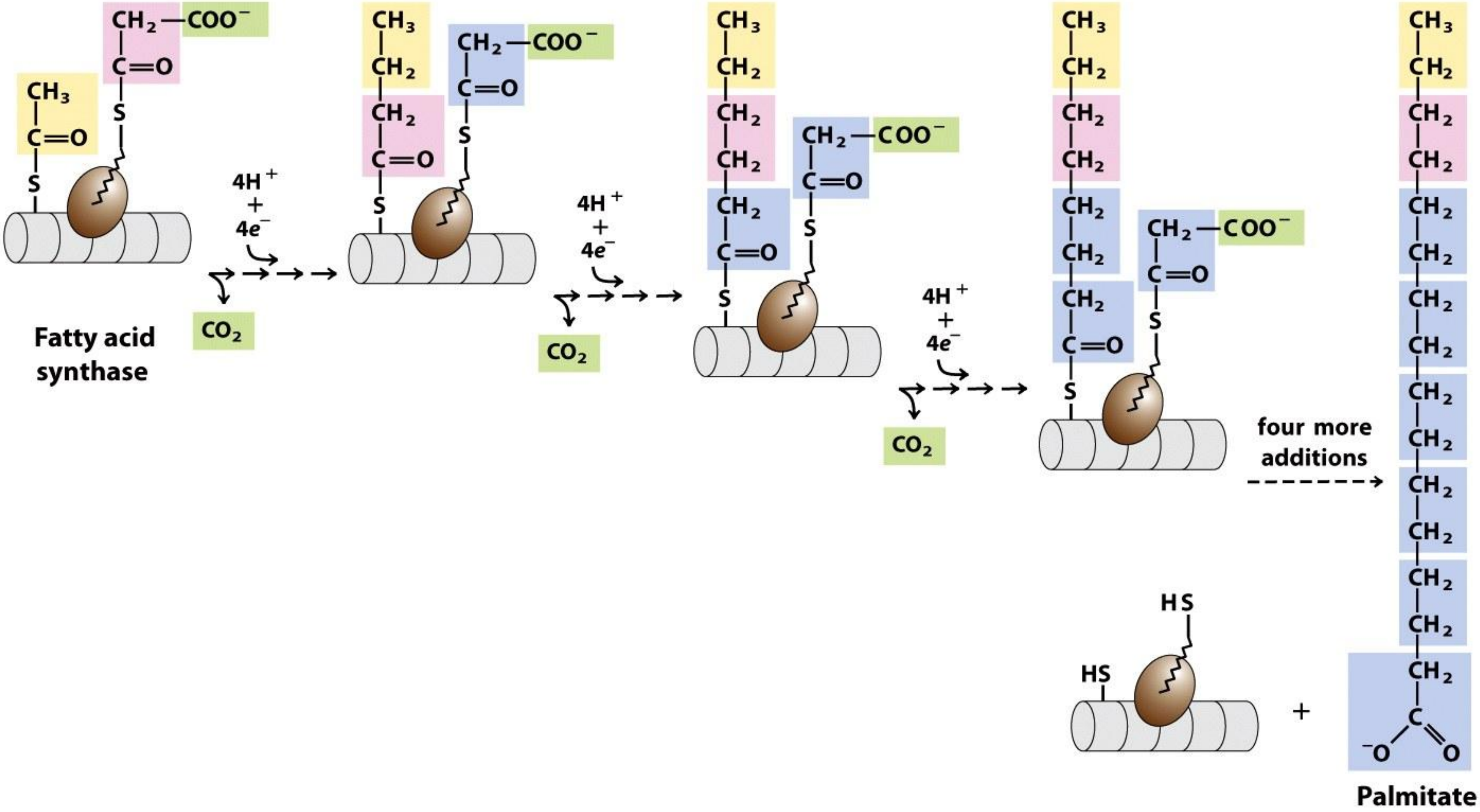

Figure 21-4
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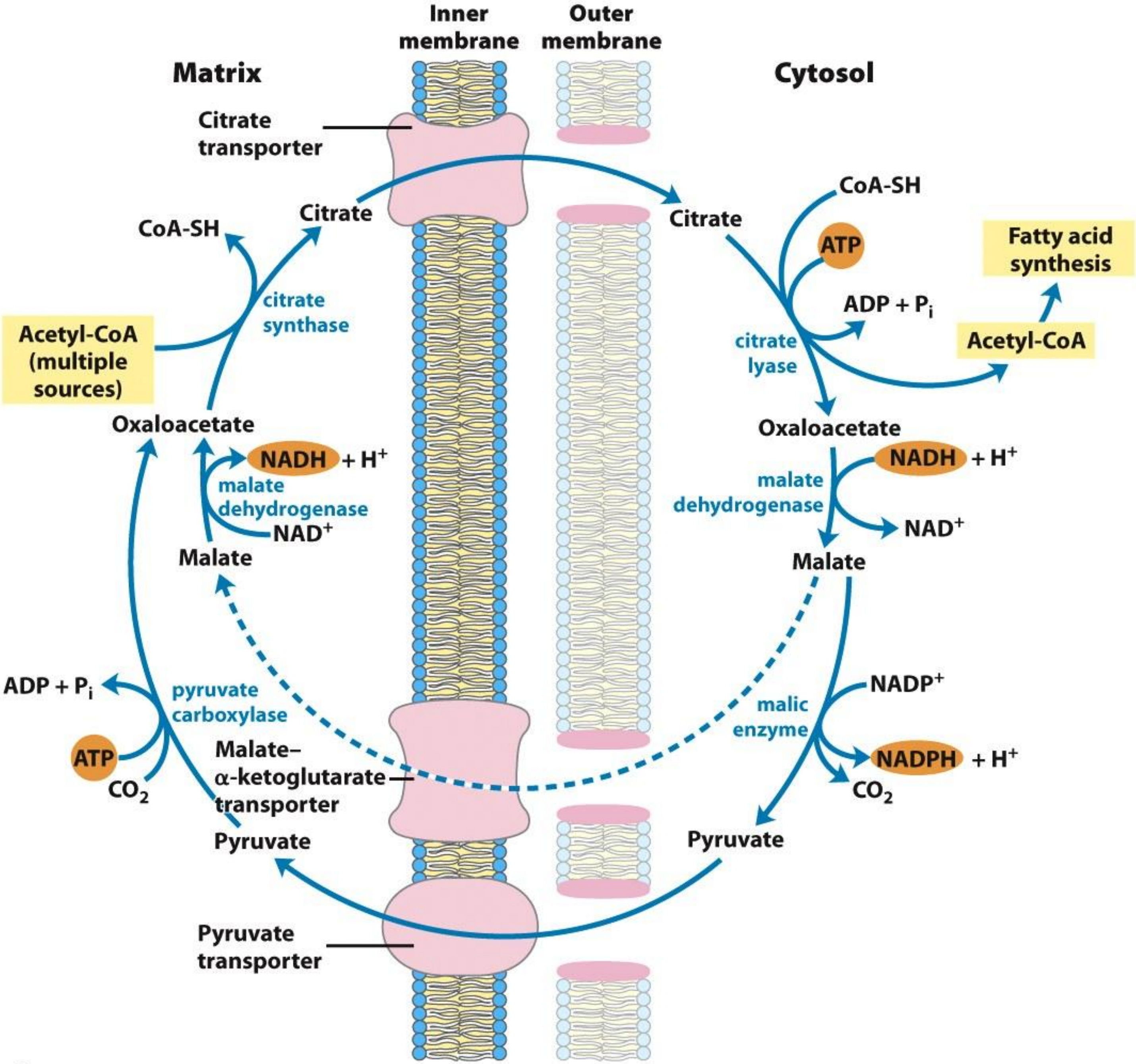

Figure 21-10

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C16, C18 and of Un-saturated Fatty Acids

- Animals can readily introduce one double bond to palmitate and stearate
- Vertebrates cannot introduce additional double bonds between C10 and methyl-terminal
- We must obtain linoleate and α-linolenate with diet; these are essential fatty acids
- Plants, algae, and some insects synthesize linoleate from oleate

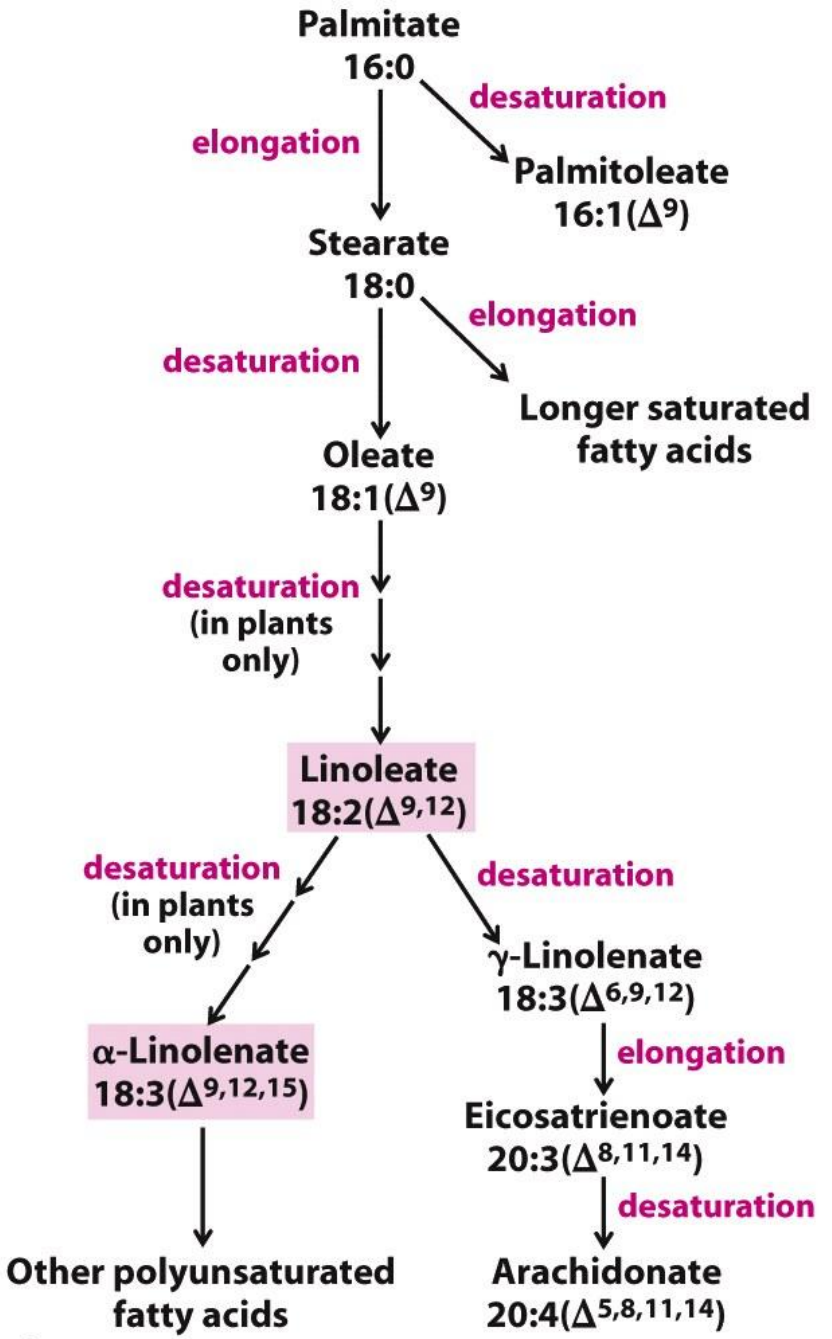

Figure 21-12

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PC-Oleate Acts as A Substrate for Plant Desaturases

- Oleic and Linoleic Acids are essential Fatty acids for mammals

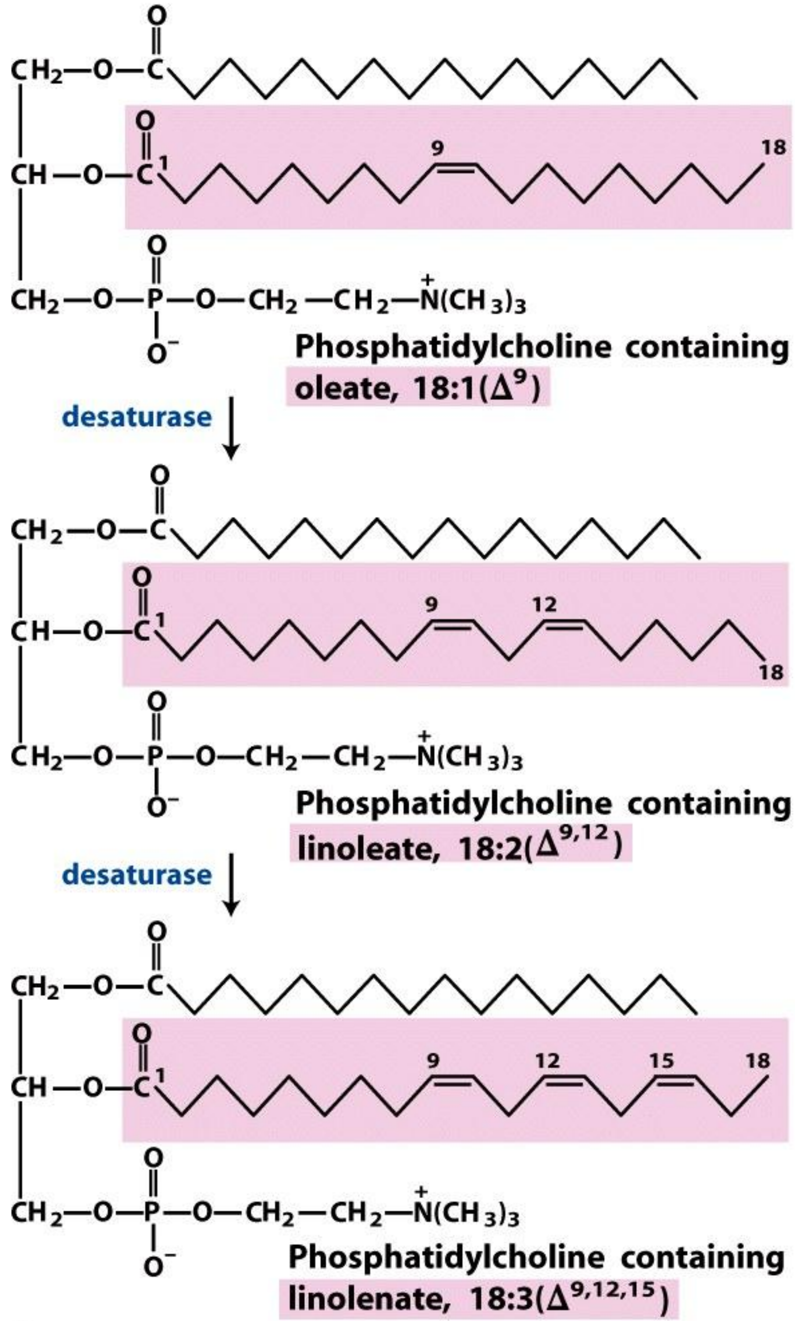
Phosphatidylcholine containing oleate, 18:1(Δ^9)
desaturase
Phosphatidylcholine containing linoleate, 18:2($\Delta^{9,12}$)
desaturase
Phosphatidylcholine containing linolenate, 18:3($\Delta^{9,12,15}$)
1
9
12
15
18

Figure 21-14
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Vertebrate Fatty Acyl Desaturase

- Non-Heme Iron - Mixed Function Oxidase
- O_2 accepts four electrons from two substrates
- Two electrons come from saturated fatty acid
- Two electrons come from ferrous state of Cytochrome *b*5

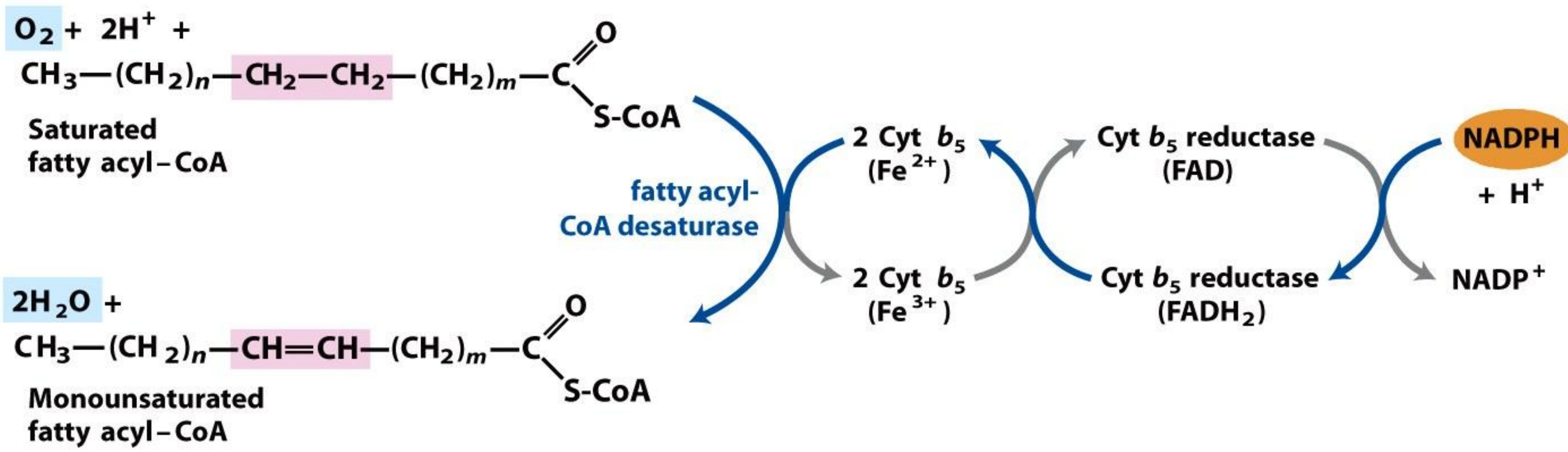
$O_2 + 2H^+ +$
$CH_3{-}(CH_2)_n{-}CH_2{-}CH_2{-}(CH_2)_m{-}C(=O){-}S\text{-}CoA$
Saturated fatty acyl–CoA
$2H_2O +$
$CH_3{-}(CH_2)_n{-}CH{=}CH{-}(CH_2)_m{-}C(=O){-}S\text{-}CoA$
Monounsaturated fatty acyl–CoA
fatty acyl-CoA desaturase
2 Cyt b_5 (Fe^{2+})
2 Cyt b_5 (Fe^{3+})
Cyt b_5 reductase (FAD)
Cyt b_5 reductase ($FADH_2$)
NADPH
$+ H^+$
$NADP^+$

Figure 21-13

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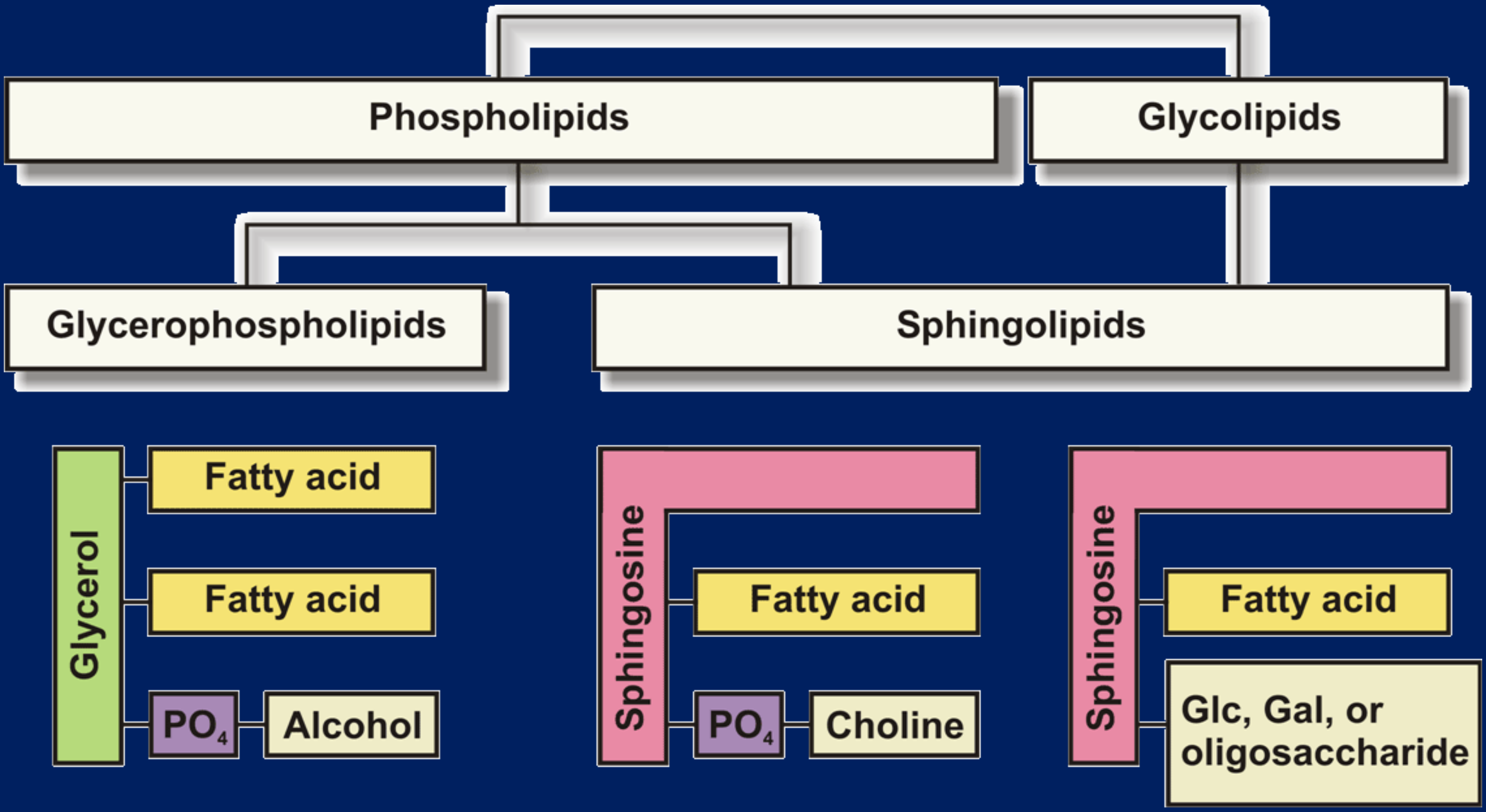
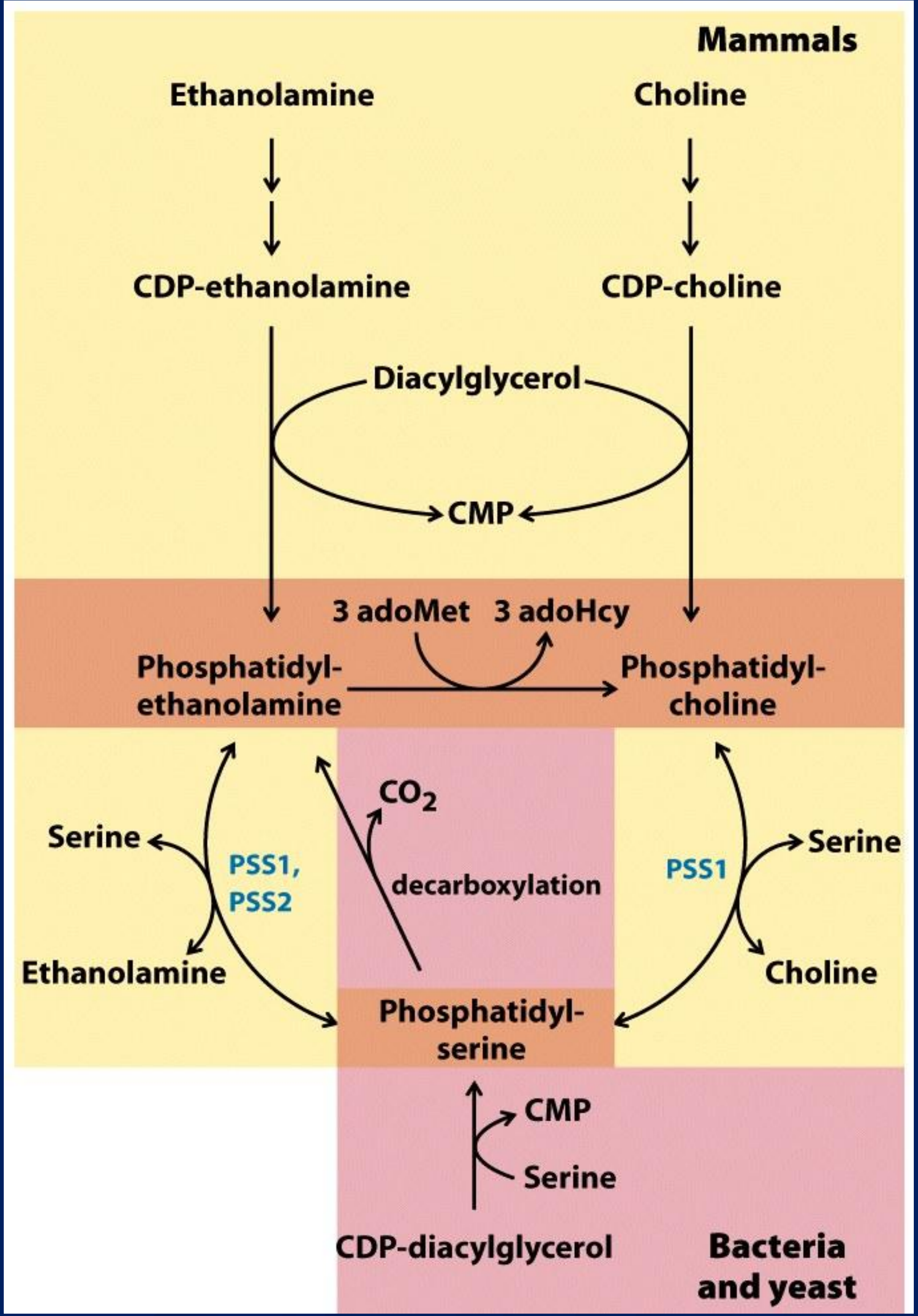
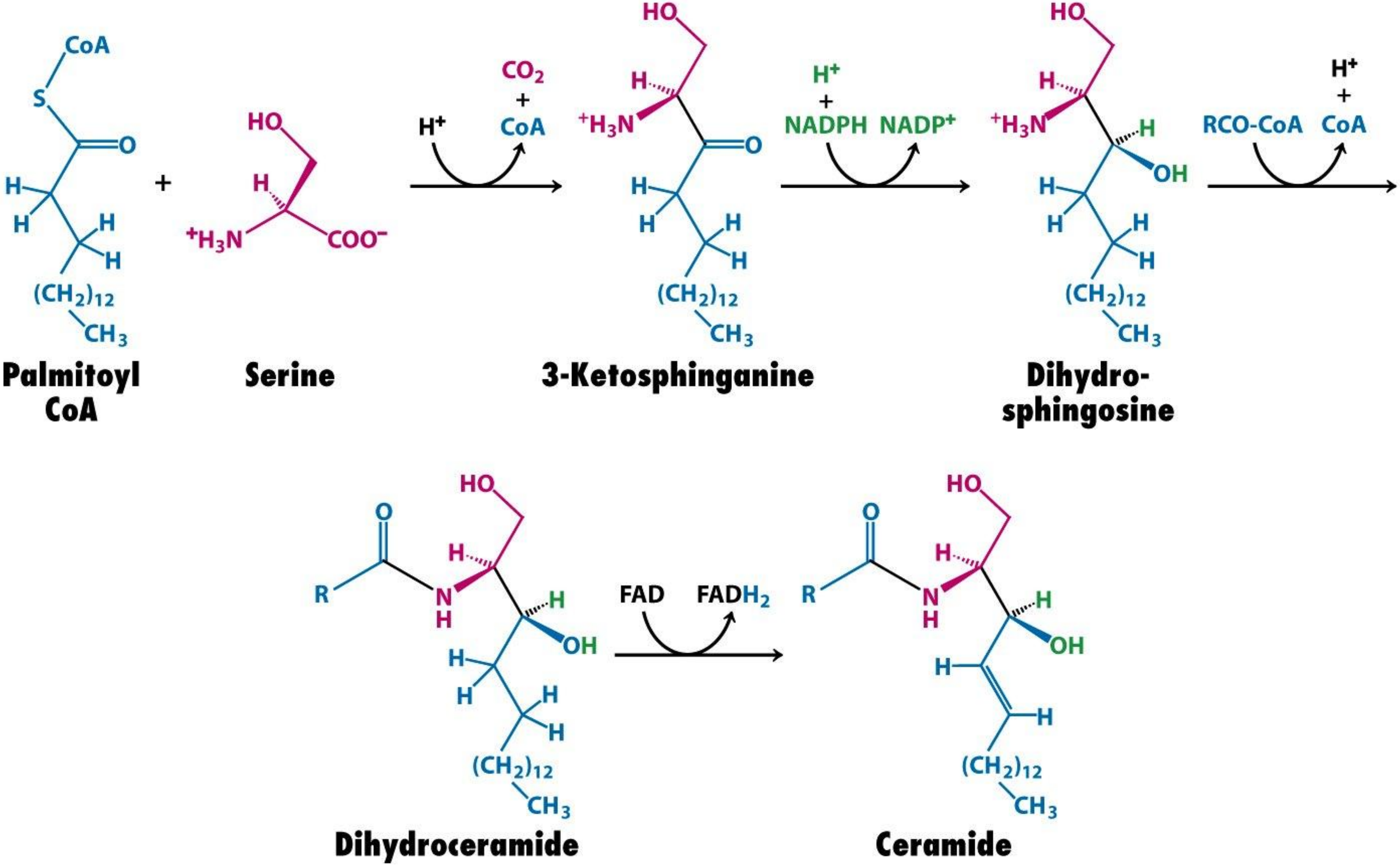
Membrane lipids



Phospholipid synthesis pathways: Summary



Biosynthesis of Ceramide



Unnumbered figure pg 737

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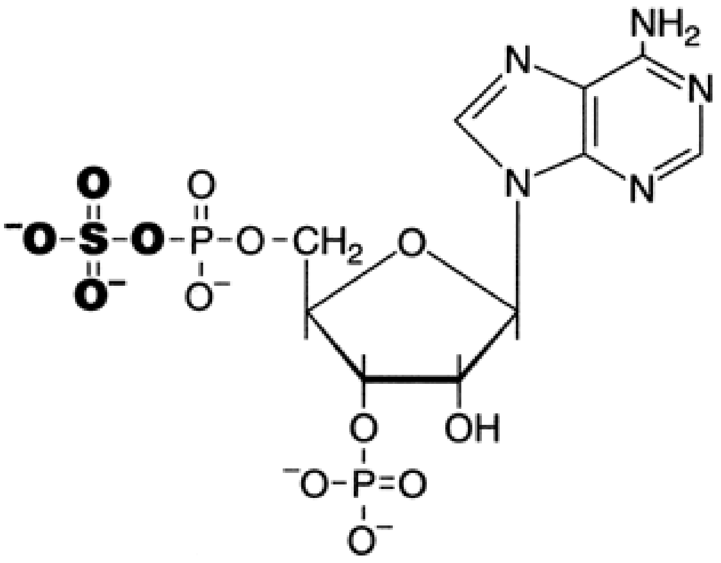
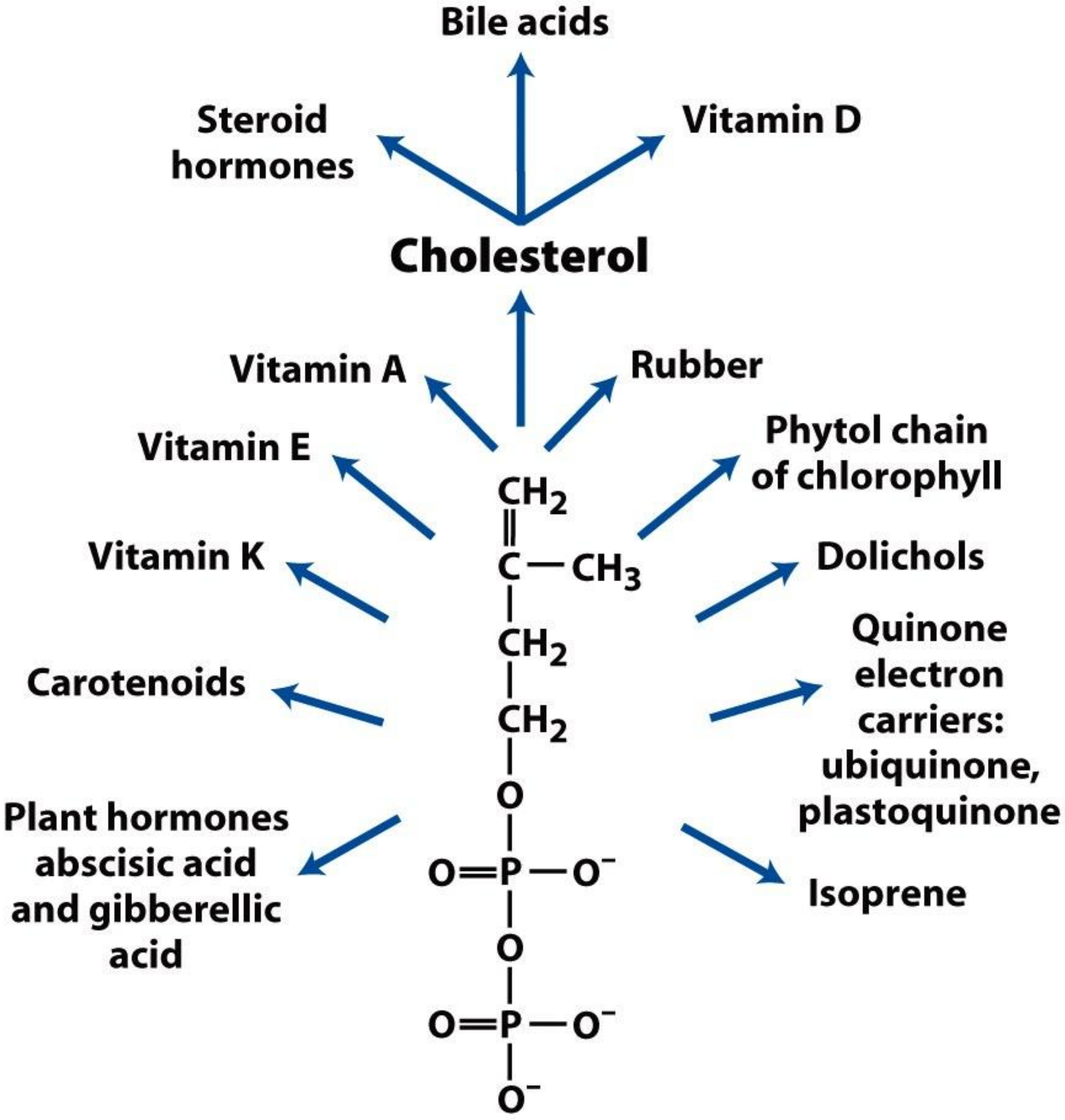
Glycolipid synthesis

- Synthesis of **glycosphingolipids** takes place **in the ER and Golgi** by the sequential addition of sugars by specific glycosyltransferases
- The sugars are activated: **UDP-Glu, UDP-Gal, CMP-NANA**
- Sulfate groups are added last by a sulfotransferase using **PAPS** (3'-phosphoadenosine-5'-phosphosulfate)



3'-Phosphoadenosine-5'-phosphosulfate

Overview of isoprenoid biosynthesis



Δ^3-Isopentenyl pyrophosphate

Figure 21-47
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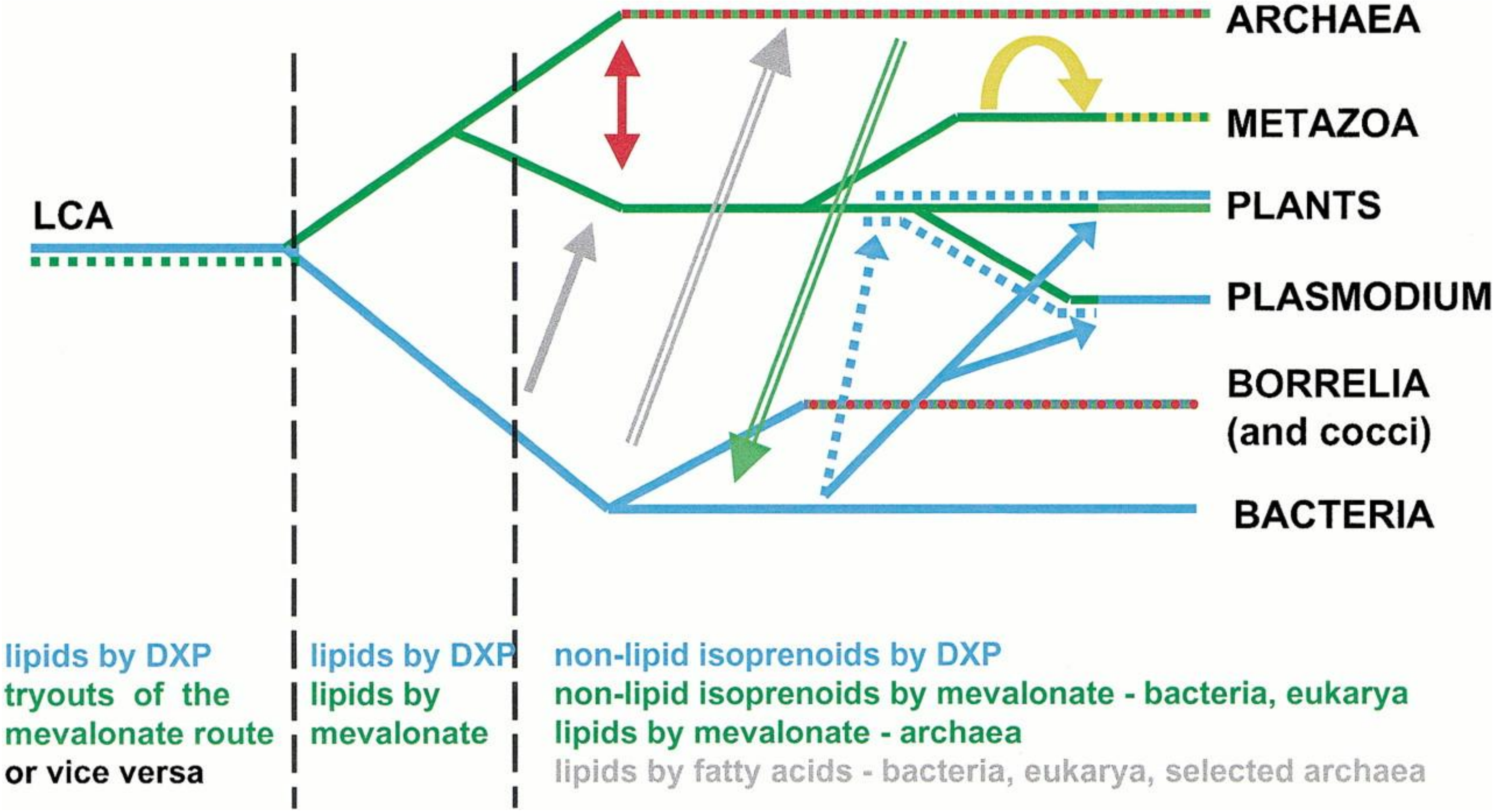
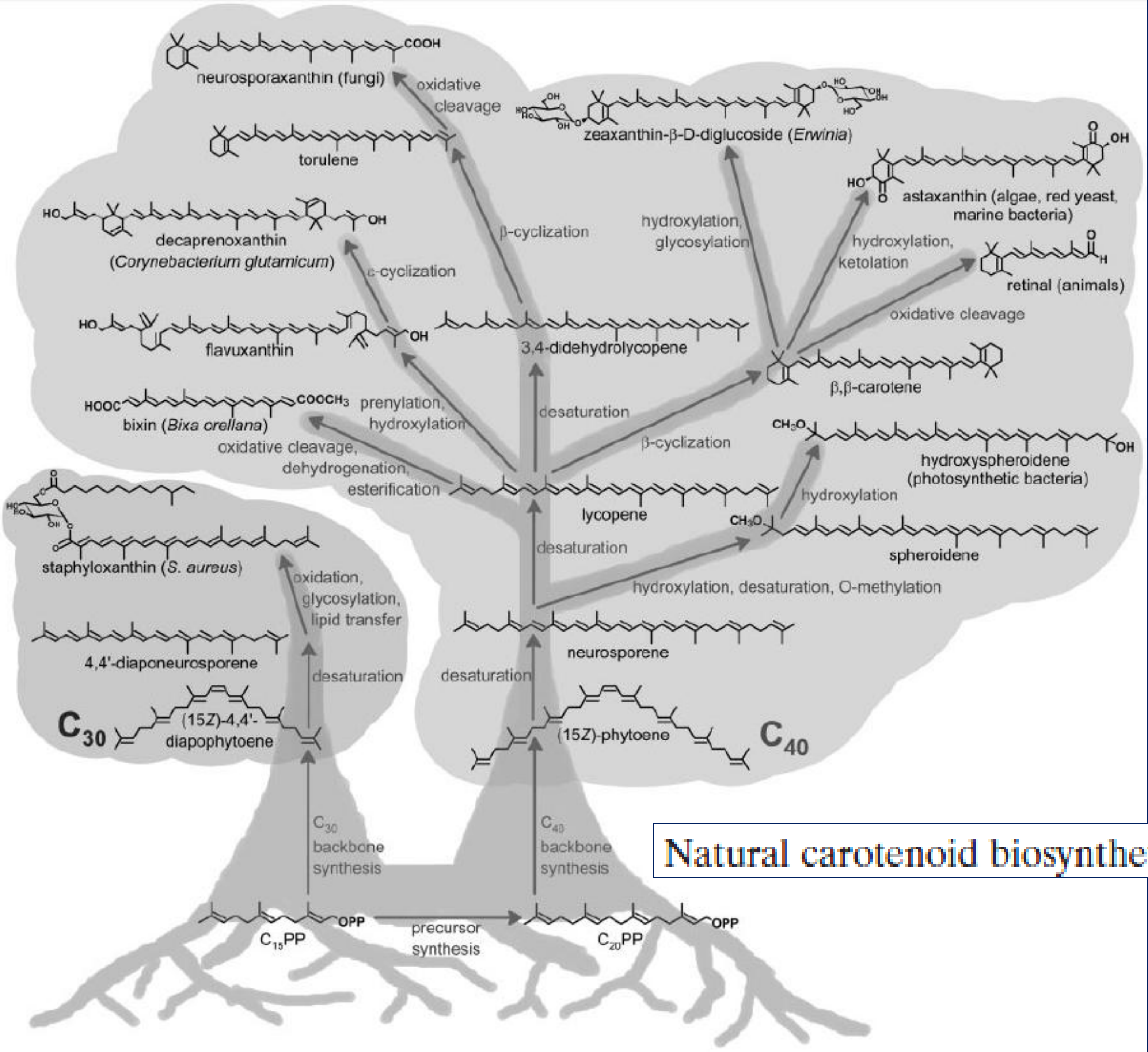
Frequent horizontal transfers in the evolution of isoprenoid biosynthesis.

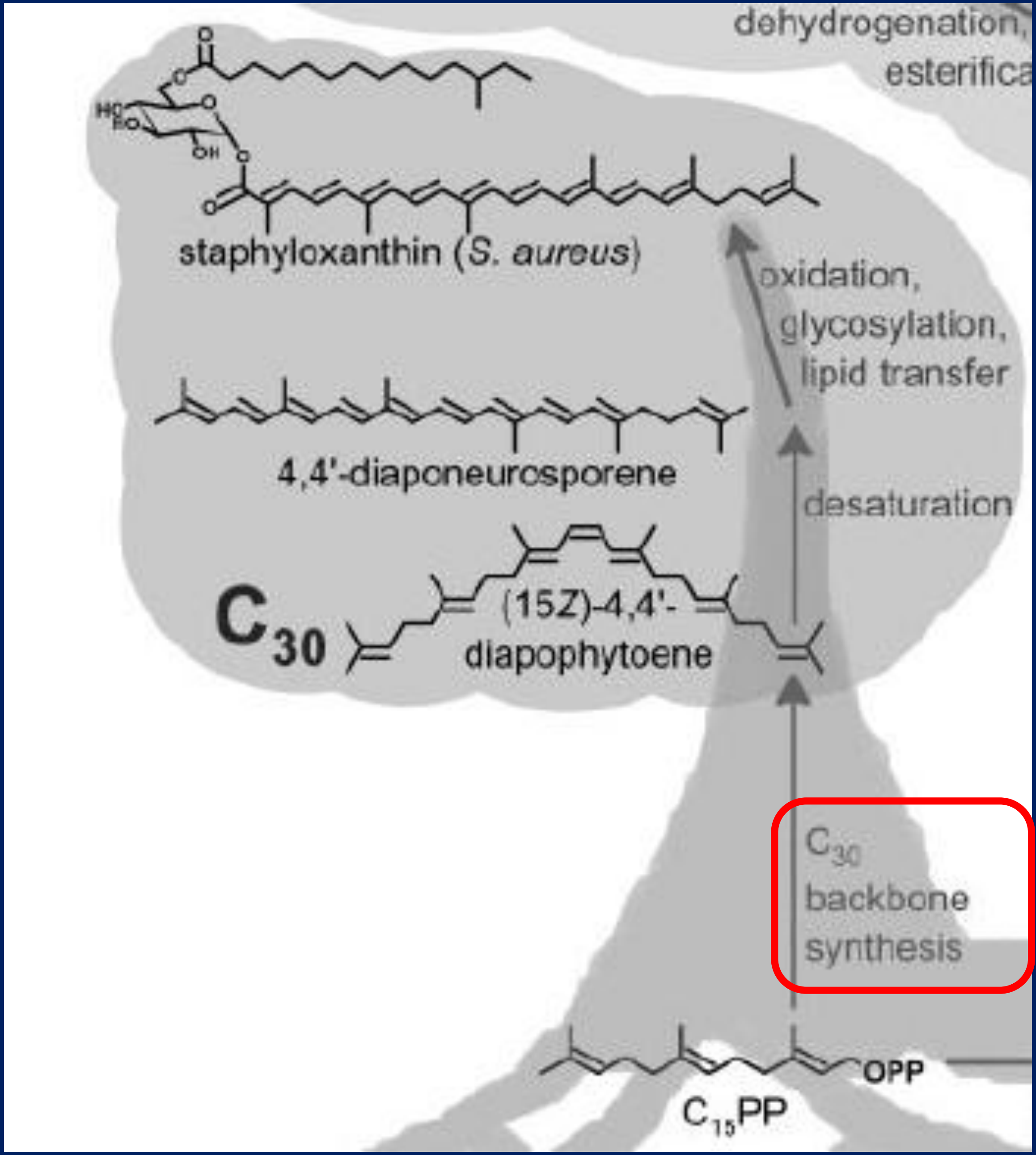

ARCHAEA
METAZOA
LCA
PLANTS
PLASMODIUM
BORRELIA (and cocci)
BACTERIA
lipids by DXP
tryouts of the mevalonate route
or vice versa
lipids by DXP
lipids by mevalonate
non-lipid isoprenoids by DXP
non-lipid isoprenoids by mevalonate - bacteria, eukarya
lipids by mevalonate - archaea
lipids by fatty acids - bacteria, eukarya, selected archaea

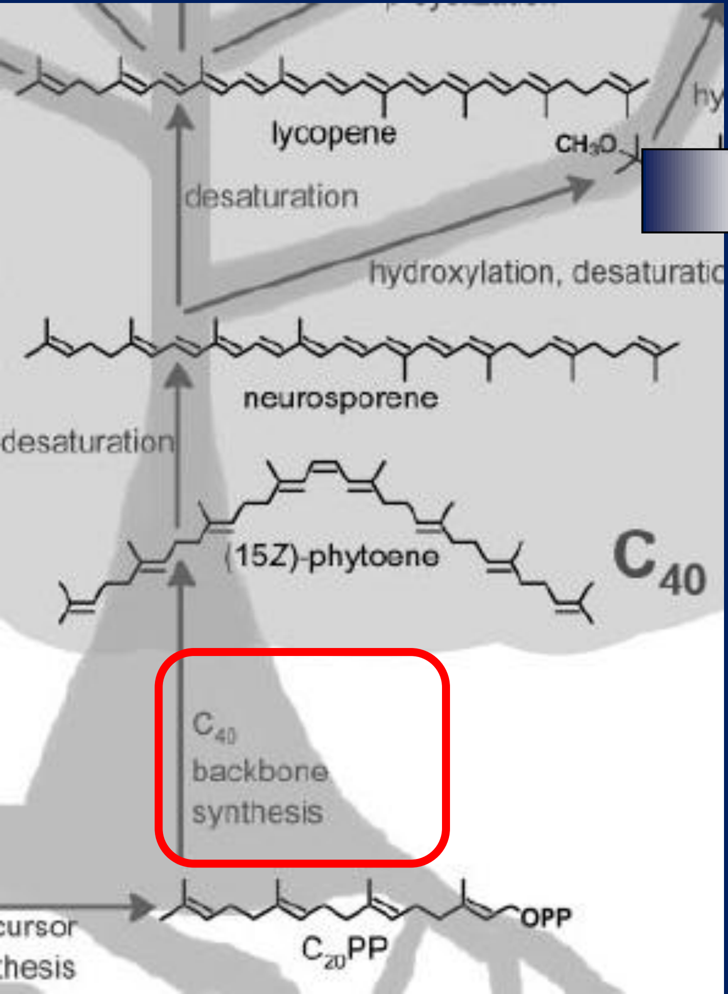
Smit A , Mushegian A Genome Res. 2000;10:1468-1484

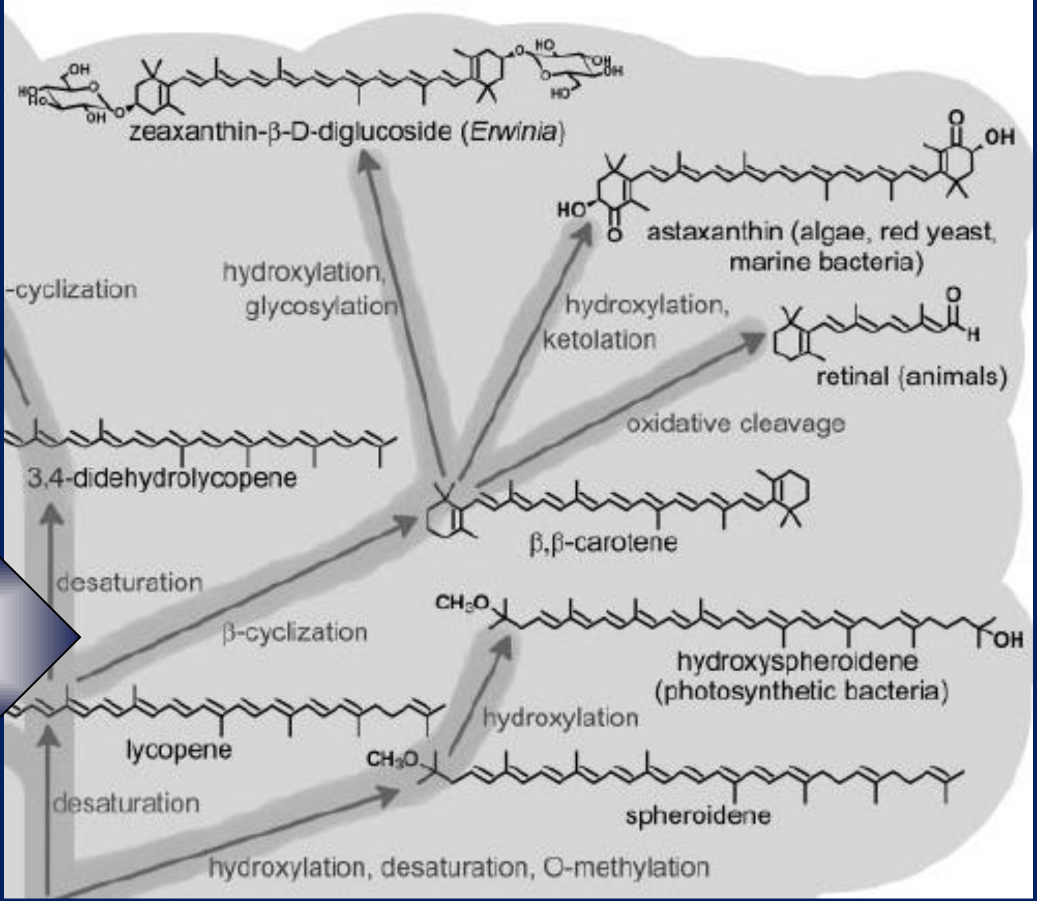
Cold Spring Harbor Laboratory Press

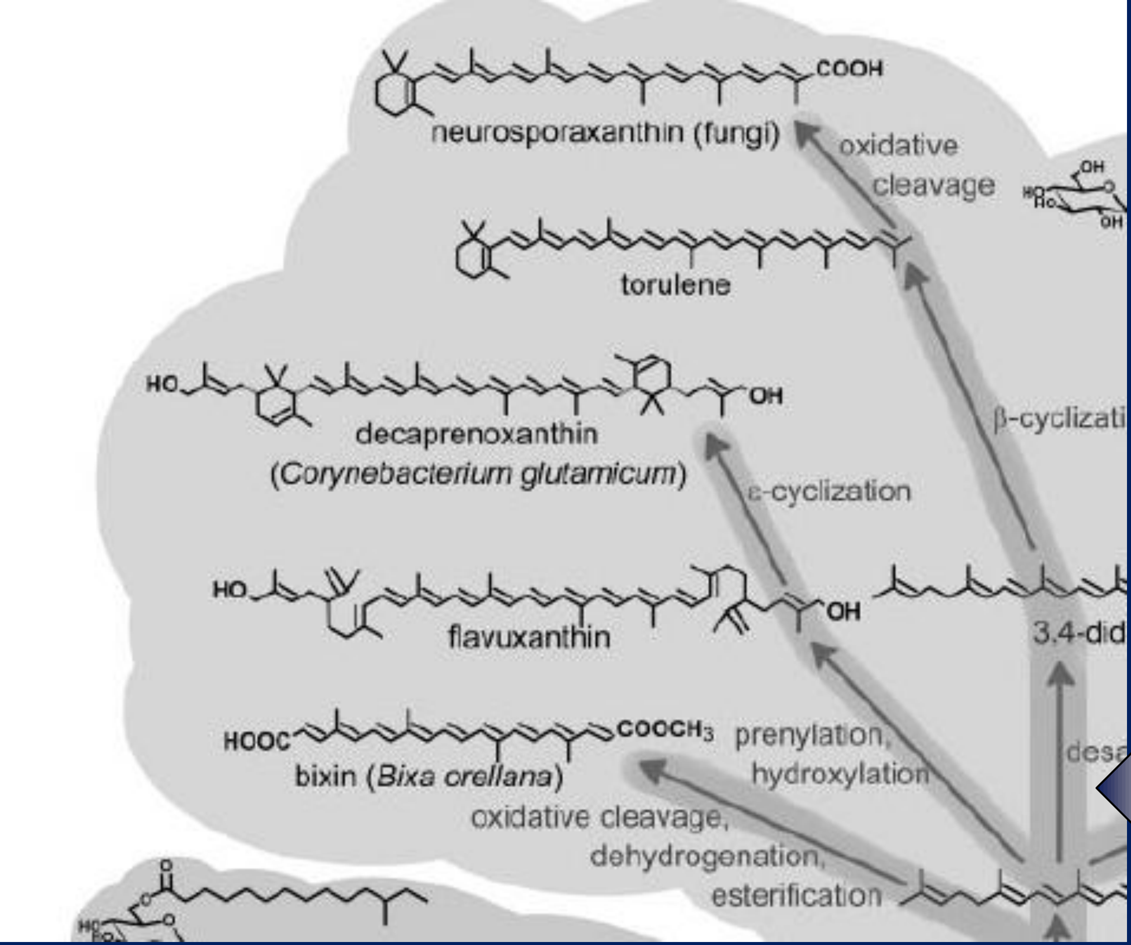
Natural carotenoid biosynthetic pathways

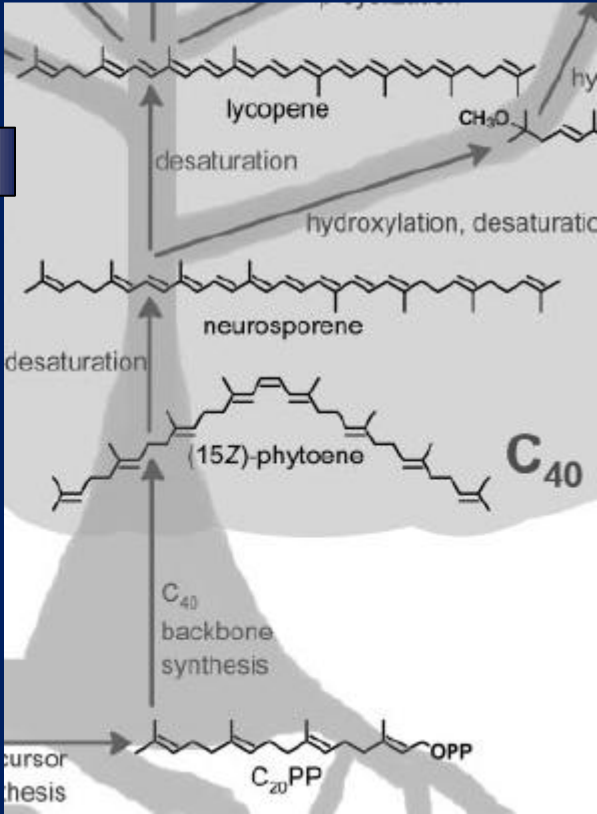

COOH
neurosporaxanthin (fungi)
oxidative cleavage
torulene
zeaxanthin-β-D-diglucoside (*Erwinia*)
HO
OH
O
astaxanthin (algae, red yeast, marine bacteria)
decaprenoxanthin (*Corynebacterium glutamicum*)
ε-cyclization
β-cyclization
hydroxylation, glycosylation
hydroxylation, ketolation
H
retinal (animals)
oxidative cleavage
flavuxanthin
3,4-didehydrolycopene
β,β-carotene
HOOC
COOCH3
bixin (*Bixa orellana*)
prenylation, hydroxylation
desaturation
β-cyclization
CH3O
hydroxyspheroidene (photosynthetic bacteria)
oxidative cleavage, dehydrogenation, esterification
lycopene
hydroxylation
spheroidene
staphyloxanthin (*S. aureus*)
desaturation
hydroxylation, desaturation, O-methylation
oxidation, glycosylation, lipid transfer
4,4'-diaponeurosporene
neurosporene
desaturation
desaturation
C30
(15Z)-4,4'-diapophytoene
(15Z)-phytoene
C40
C30 backbone synthesis
C40 backbone synthesis
OPP
C15PP
precursor synthesis
OPP
C20PP


dehydrogenation,
esterifica
O
HO
HO
OH
staphyloxanthin (*S. aureus*)
oxidation,
glycosylation,
lipid transfer
4,4'-diaponeurosporene
desaturation
C_{30}
(15*Z*)-4,4'-diapophytoene
C_{30} backbone synthesis
OPP
$C_{15}PP$


lycopene
CH_3O
desaturation
hydroxylation, desaturatio
neurosporene
desaturation
(15Z)-phytoene
C_{40}
C_{40} backbone synthesis
cursor
thesis
OPP
$C_{20}PP$


zeaxanthin-β-D-diglucoside (*Erwinia*)
astaxanthin (algae, red yeast, marine bacteria)
HO
OH
-cyclization
hydroxylation, glycosylation
hydroxylation, ketolation
retinal (animals)
oxidative cleavage
3,4-didehydrolycopene
β,β-carotene
desaturation
β-cyclization
CH_3O
OH
hydroxyspheroidene (photosynthetic bacteria)
lycopene
hydroxylation
CH_3O
desaturation
spheroidene
hydroxylation, desaturation, O-methylation


COOH
neurosporaxanthin (fungi)
oxidative cleavage
OH
HO
torulene
β-cyclizati
HO
OH
decaprenoxanthin (Corynebacterium glutamicum)
ε-cyclization
HO
OH
flavuxanthin
3,4-did
HOOC
COOCH$_3$
bixin (Bixa orellana)
prenylation, hydroxylation
desa
oxidative cleavage, dehydrogenation, esterification
O
HO


lycopene
hy
CH$_3$O
desaturation
hydroxylation, desaturatio
neurosporene
desaturation
(15Z)-phytoene
C$_{40}$
C$_{40}$ backbone synthesis
ursor
hesis
C$_{20}$PP
OPP

Biosynthesis of Cholesterol

- Summary

1. Acetyl CoA => Mevalonate
2. Mevalonate => Isoprenes
3. 6 isoprenes => squalene
4. Squalene to lanosterol

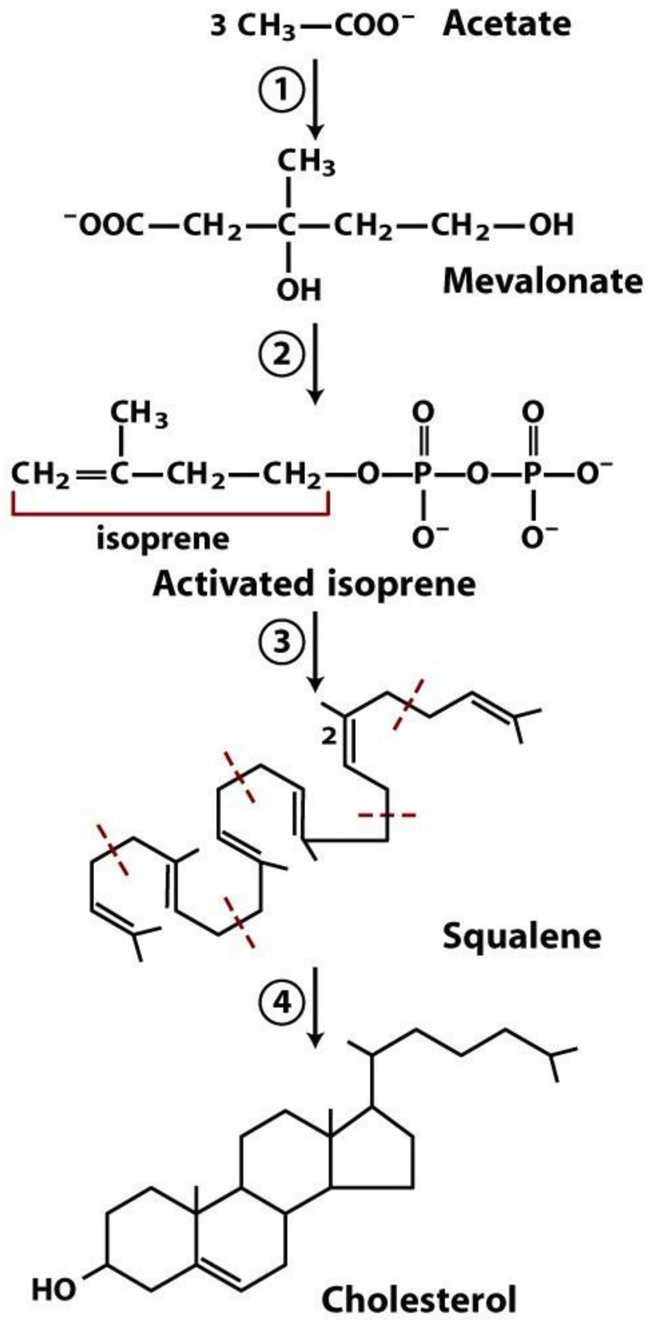


Figure 21-33
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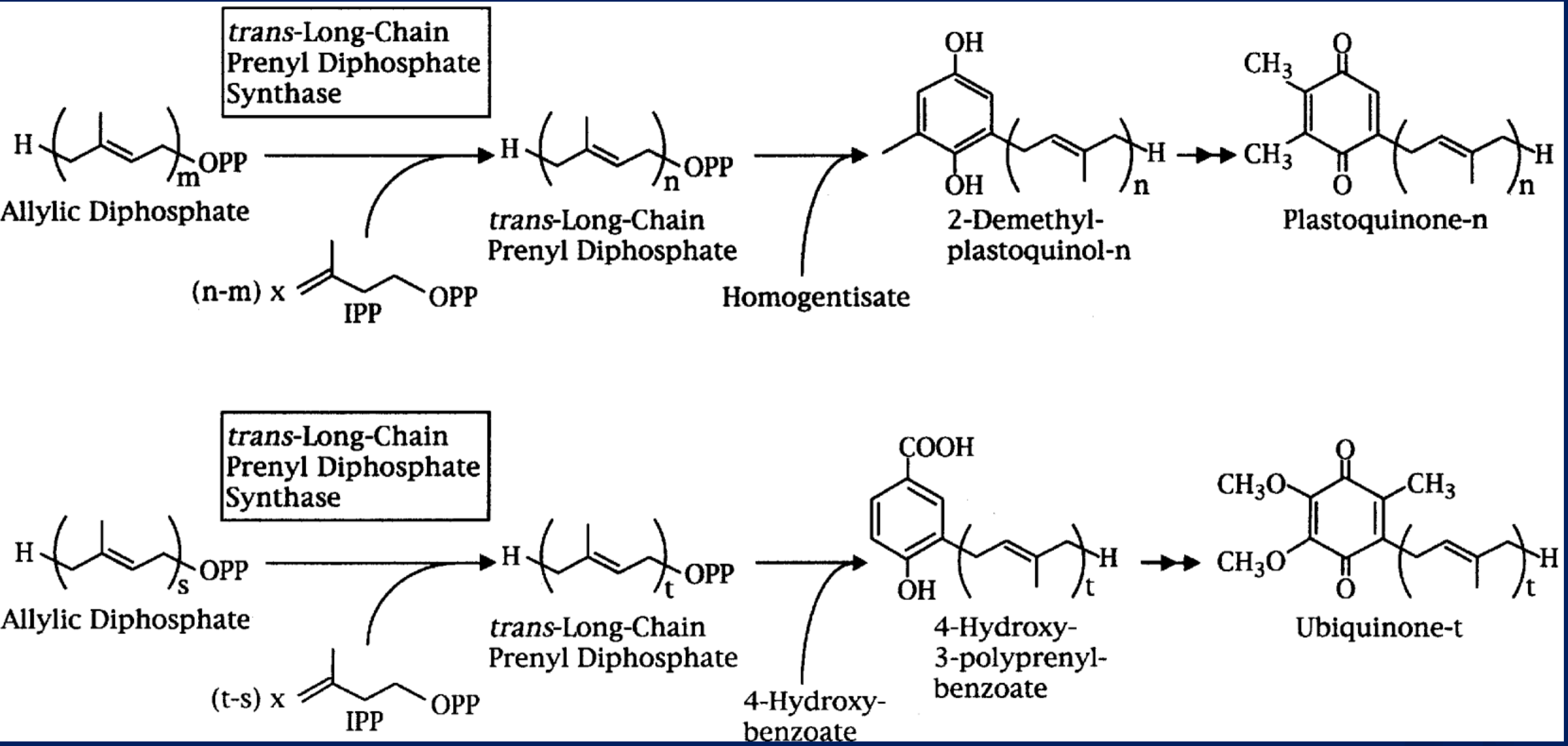
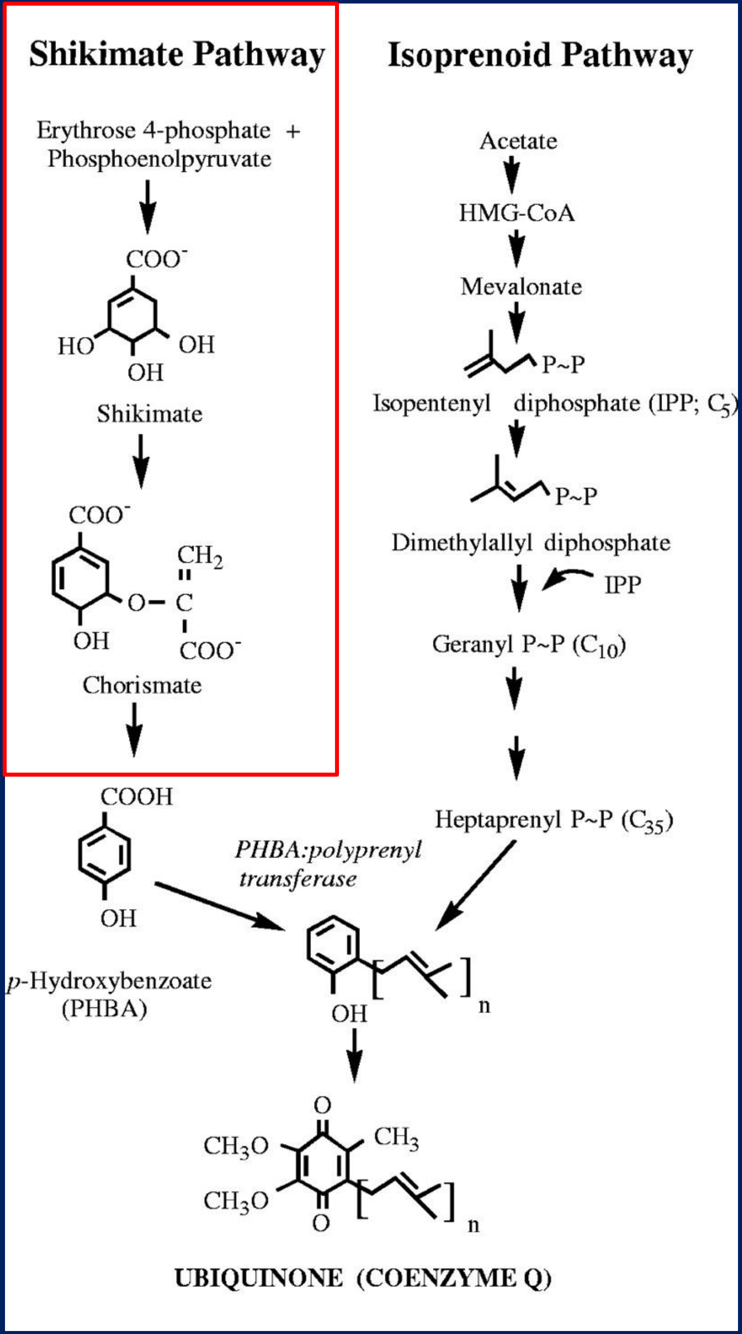
Biosynthesis of quinones (UQ; PQ)


trans-Long-Chain Prenyl Diphosphate Synthase
H
OPP
m
Allylic Diphosphate
(n-m) x
IPP
OPP
H
OPP
n
trans-Long-Chain Prenyl Diphosphate
Homogentisate
OH
OH
H
n
2-Demethyl-plastoquinol-n
CH3
CH3
O
O
H
n
Plastoquinone-n
trans-Long-Chain Prenyl Diphosphate Synthase
H
OPP
s
Allylic Diphosphate
(t-s) x
IPP
OPP
H
OPP
t
trans-Long-Chain Prenyl Diphosphate
4-Hydroxy-benzoate
COOH
OH
H
t
4-Hydroxy-3-polyprenyl-benzoate
CH3O
CH3O
CH3
O
O
H
t
Ubiquinone-t



Shikimate Pathway

Erythrose 4-phosphate + Phosphoenolpyruvate

COO^-

HO OH OH

Shikimate

COO^- CH_2 O C COO^- OH

Chorismate

COOH OH

p-Hydroxybenzoate (PHBA)

Isoprenoid Pathway

Acetate

HMG-CoA

Mevalonate

P~P

Isopentenyl diphosphate (IPP; C_5)

P~P

Dimethylallyl diphosphate

IPP

Geranyl P~P (C_{10})

Heptaprenyl P~P (C_{35})

PHBA:polyprenyl transferase

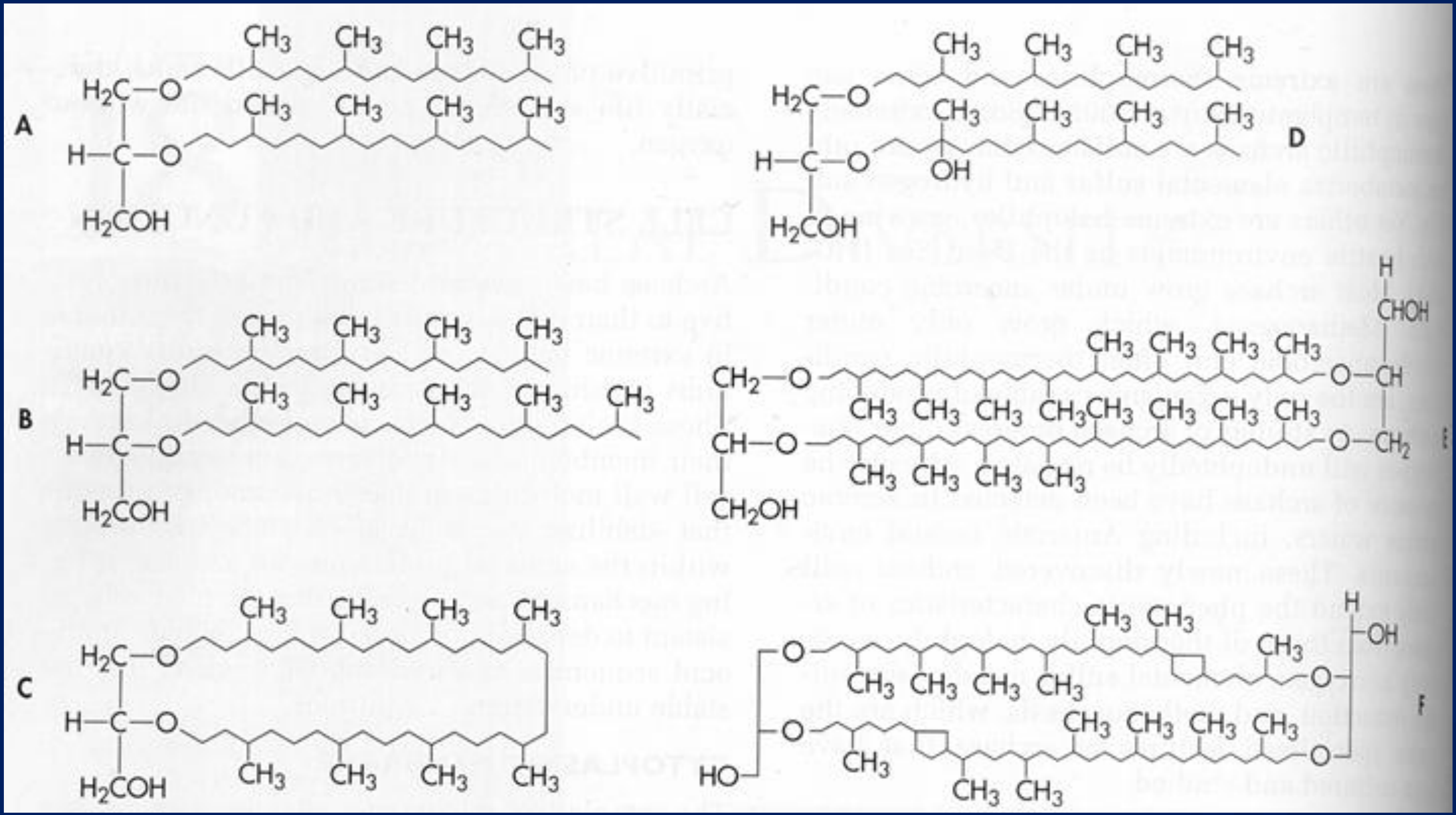
OH n

O CH_3O CH_3 CH_3O O n

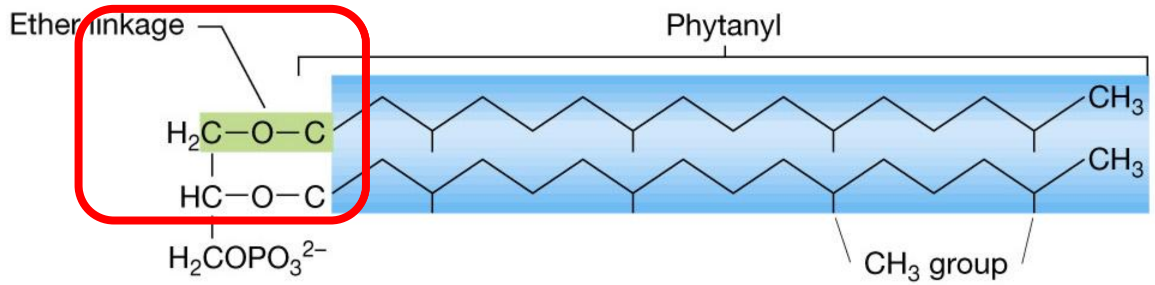
UBIQUINONE (COENZYME Q)

Особенности синтеза липидов у 3-х доменов жизни

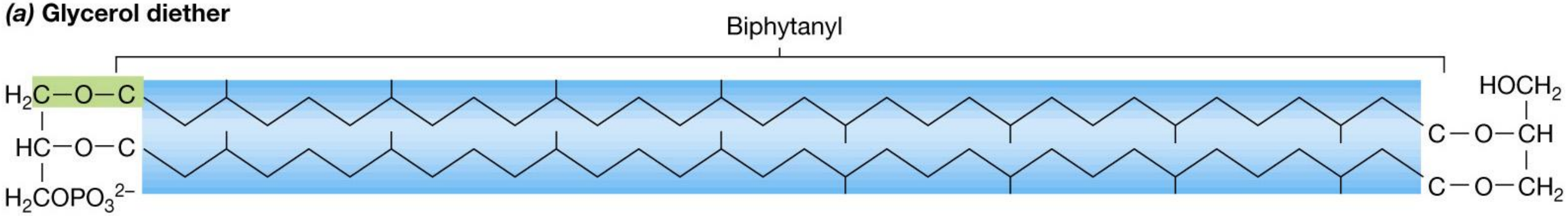
Особенности липидов архей



Archaeal lipids

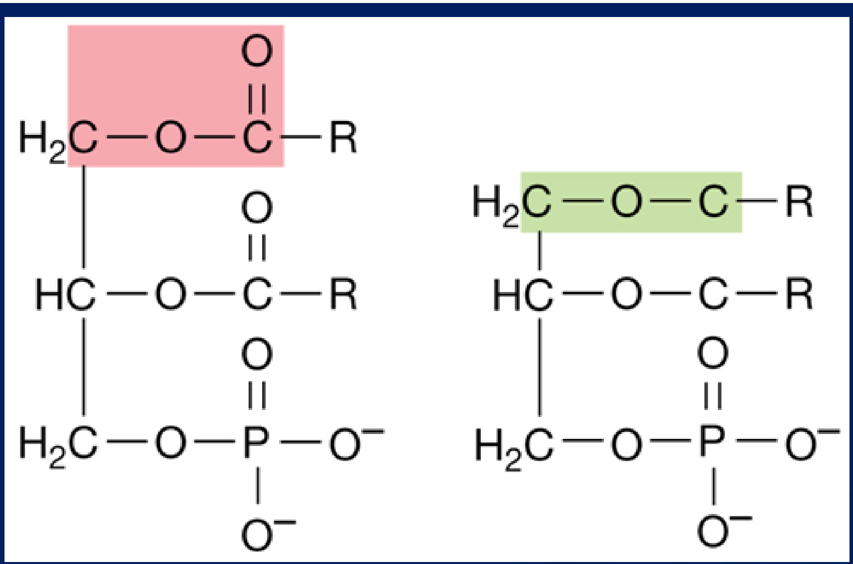


***(a)* Glycerol diether**



***(b)* Diglycerol tetraether**

Ester linkage


$H_2C-O-\overset{O}{\overset{\|}{C}}-R$
$HC-O-\overset{O}{\overset{\|}{C}}-R$
$H_2C-O-\overset{O}{\overset{\|}{P}}-O^-$
O^-
$H_2C-O-C-R$
$HC-O-C-R$
$H_2C-O-\overset{O}{\overset{\|}{P}}-O^-$
O^-

Ether Linkage

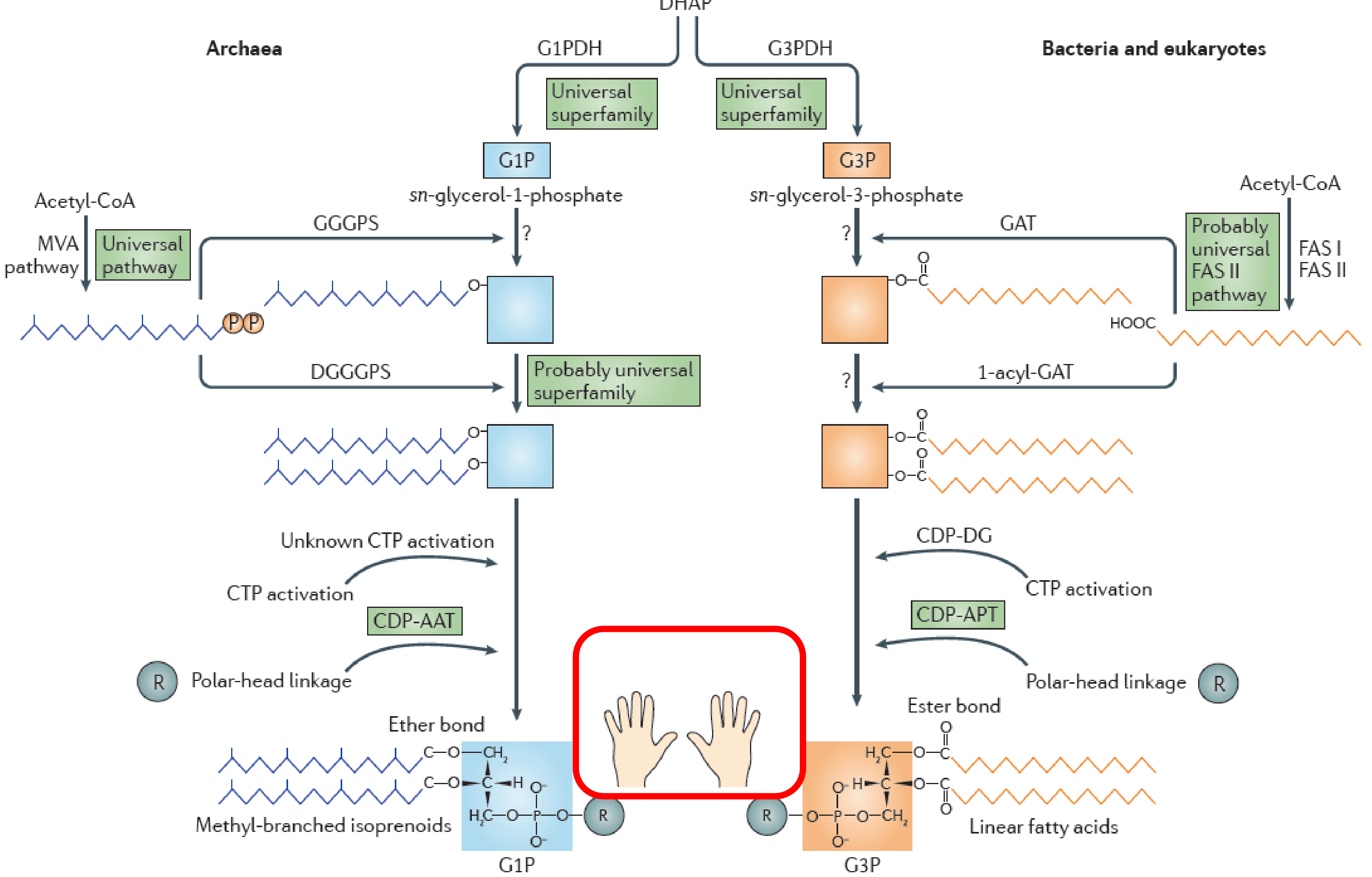
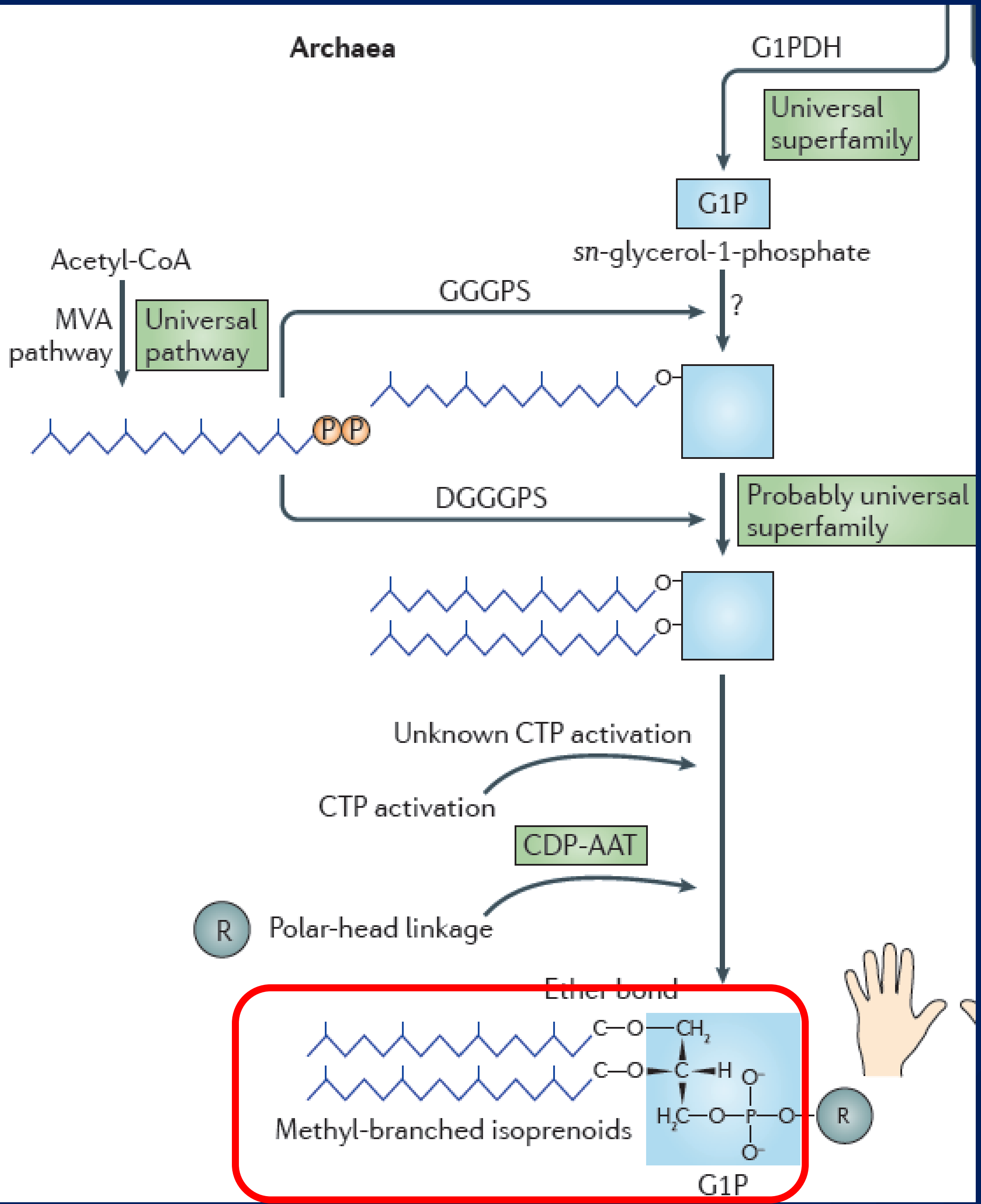


Figure 1 | **Phospholipid biosynthesis pathways in archaea, bacteria and eukaryotes.** Phospholipid components and the enzymes that synthesize them are different in modern archaea versus modern bacteria and eukaryotes. For some steps in the pathways, there is phylogenomic evidence either supporting the hypothesis that homologous enzymes carried out a particular step in the cenancestor (universal proteins or pathways) or indicating that the presence of the relevant enzymes in the cenancestor cannot be excluded (probably universal proteins or pathways). Cytidine diphosphate-alcohol archaetidyltransferase (CDP-AAT) and CDP-alcohol phosphatidyltransferase (CDP-APT) are homologous in the two pathways. Polar head radicals can be serine, ethanolamine or glycerol, among others. A question mark indicates that information is unknown. CDP-DG, CDP-diacylglycerol synthase; CTP, cytidine triphosphate; DGGGPS, digeranylgeranylglyceryl phosphate synthase; DHAP, dihydroxyacetone phosphate; G1P, *sn*-glycerol-1-phosphate; G1PDH, G1P dehydrogenase; G3P, *sn*-glycerol-3-phosphate; G3PDH, G3P dehydrogenase; GAT, G1P acyltransferase; GGGPS, geranylgeranylglyceryl phosphate synthase; FAS, fatty acid synthesis; MVA, mevalonate.



Archaea

G1PDH

Universal superfamily

G1P

sn-glycerol-1-phosphate

Acetyl-CoA

MVA pathway

Universal pathway

GGGPS

?

DGGGPS

Probably universal superfamily

Unknown CTP activation

CTP activation

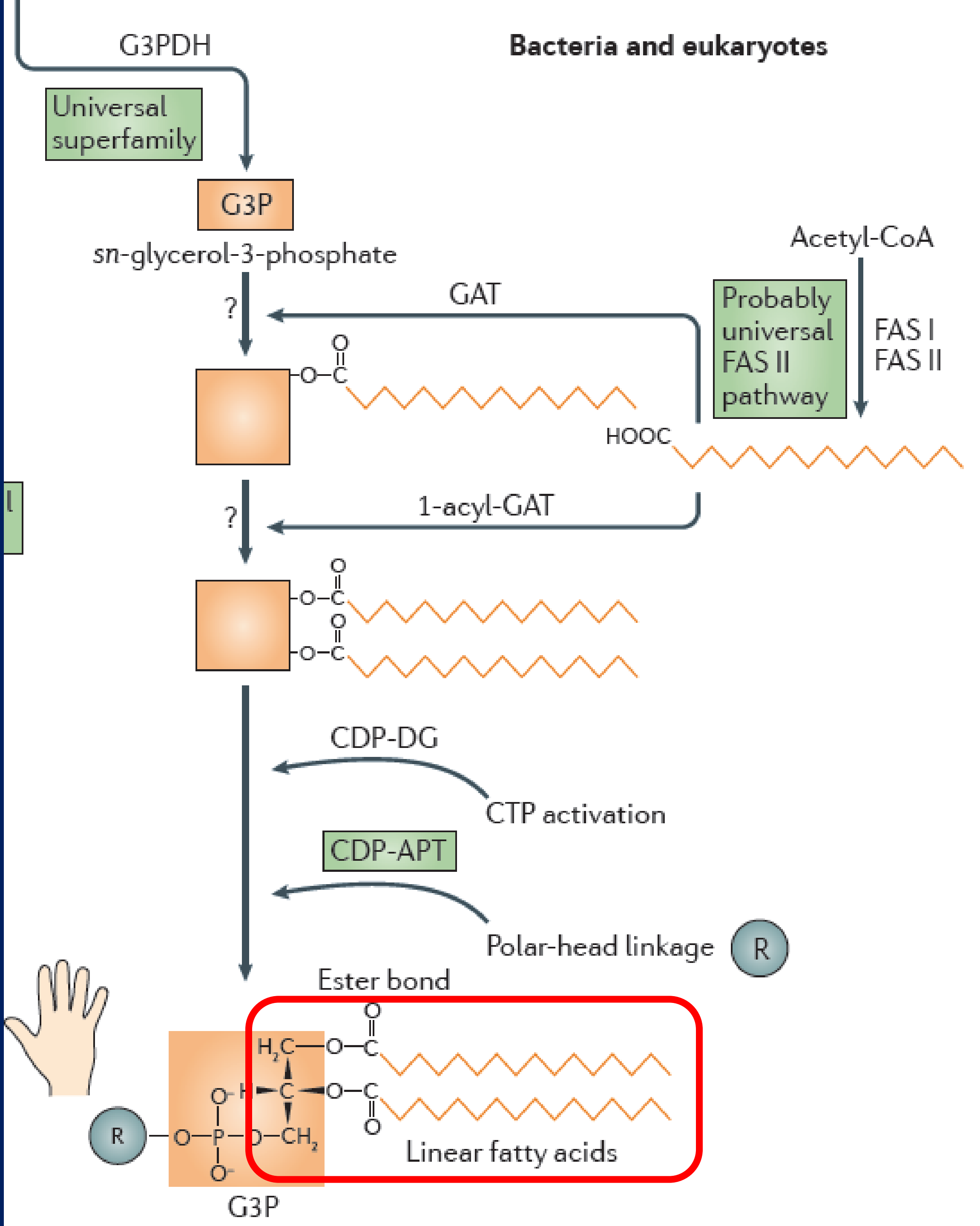
CDP-AAT

Polar-head linkage

Ether bond

Methyl-branched isoprenoids

G1P



Bacteria and eukaryotes

G3PDH

Universal superfamily

G3P

sn-glycerol-3-phosphate

?

GAT

Acetyl-CoA

Probably universal FAS II pathway

FAS I
FAS II

HOOC

?

1-acyl-GAT

CDP-DG

CTP activation

CDP-APT

Polar-head linkage

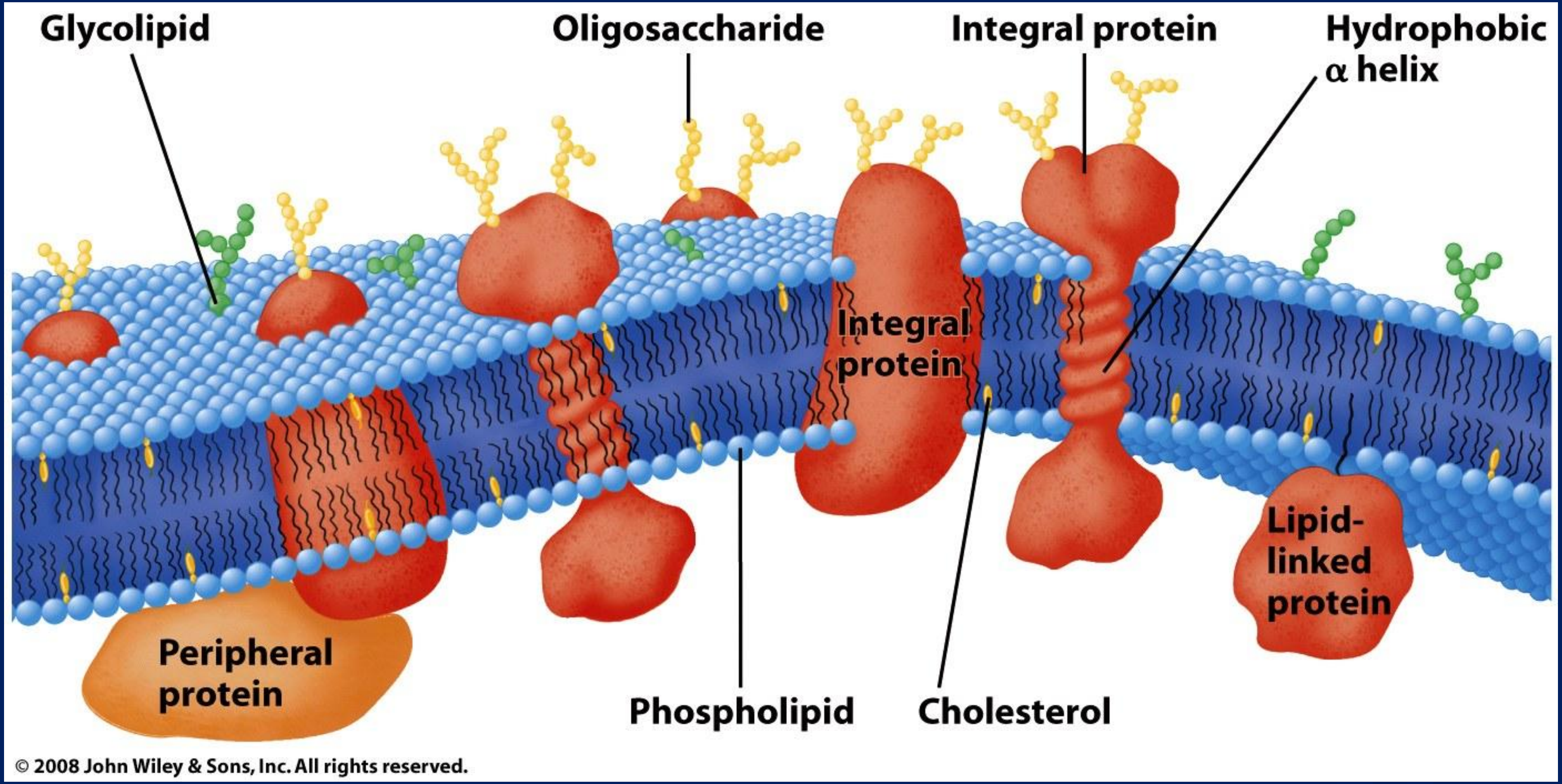
R

Ester bond

Linear fatty acids

G3P

Синтез и сборка Кл мембран



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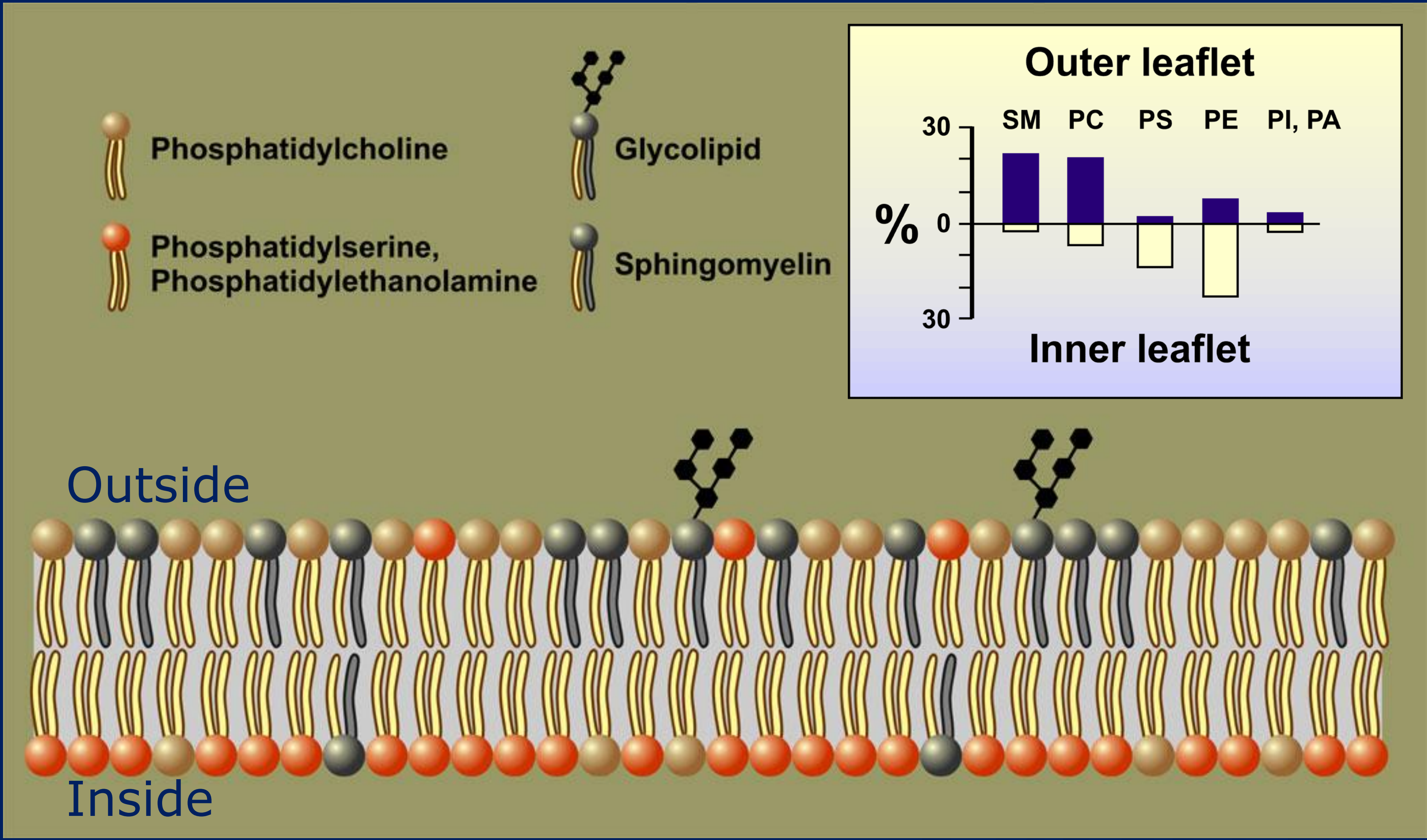
Phospholipids are distributed asymmetrically in the plasma membrane



The Chemical Composition of Membranes (plasma membrane of human erythrocytes)

- The Asymmetry of Membrane Lipids
  - 1. Inner and outer membrane leaflets of various membranous structures, of particular significance in the plasma membrane, have different lipid compositions.
  - 2. Provides different physico-chemical properties appropriate for different interactions
  - 3. Membrane lipids move easily within a leaflet but, **with the exception of cholesterol**, only rarely "flip-flop"

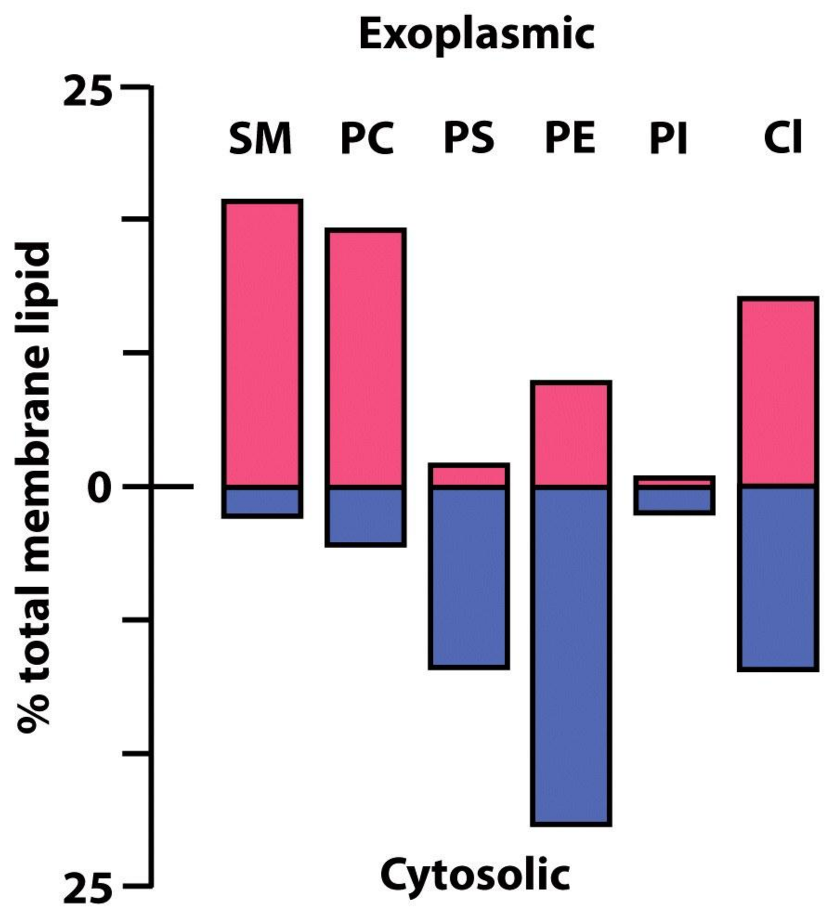
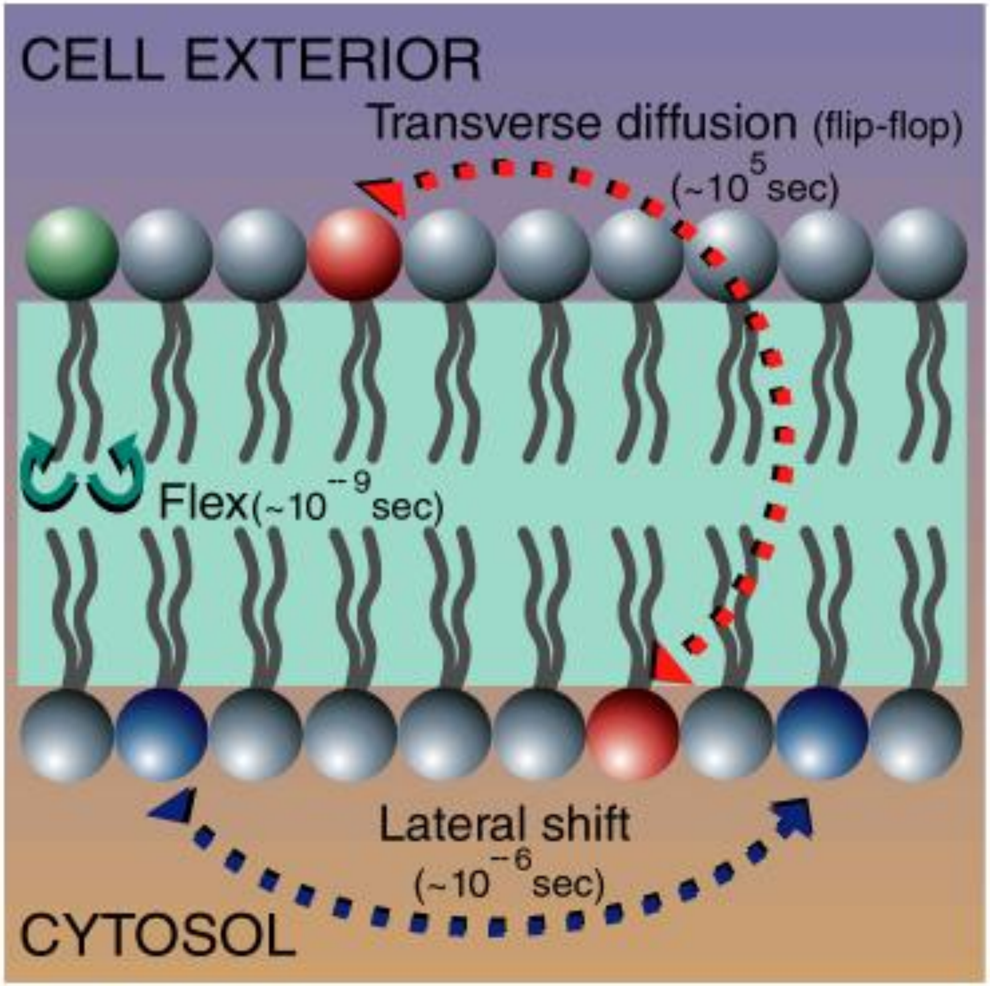


Fig. 4.10 The asymmetric distribution of phospholipids (and cholesterol) in the plasma membrane of human erythrocytes) (SM, sphingomyelin, PC, phosphatidylcholine, PS, phosphatidylserine, PE, phosphatidylethanolamine, PI, Phosphatidylinositol, Cl, cholesterol)

Possible movements of phospholipids in a membrane



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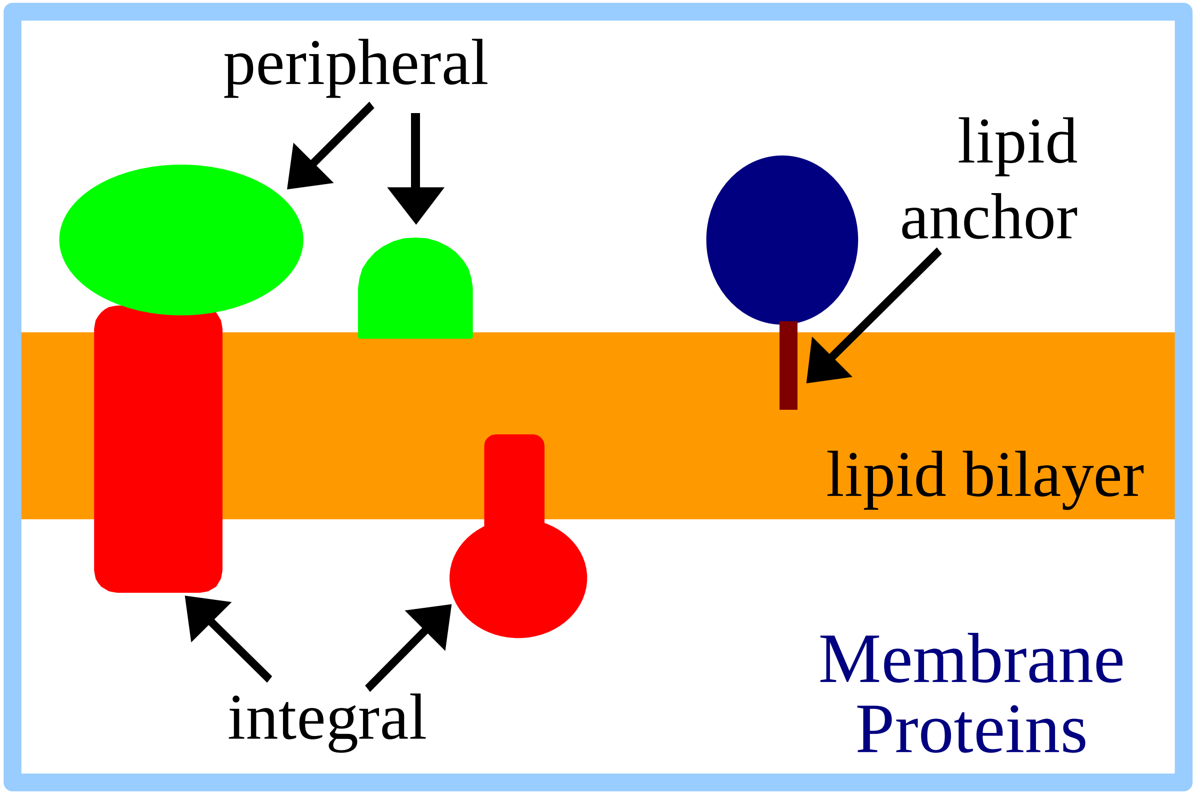
Whereas phospholipids move from one leaflet to another (flip-flop) at a very slow rate (except when there is new synthesis, e.g. flippase), phospholipids diffuse laterally within leaflet rapidly.

Membrane proteins may be classified as:

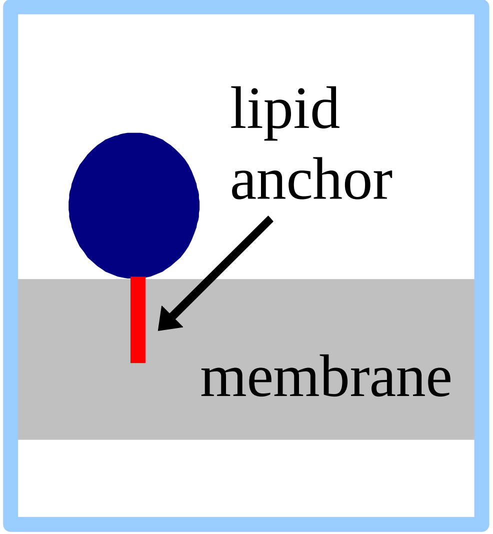
- peripheral
- having a lipid anchor
- integral

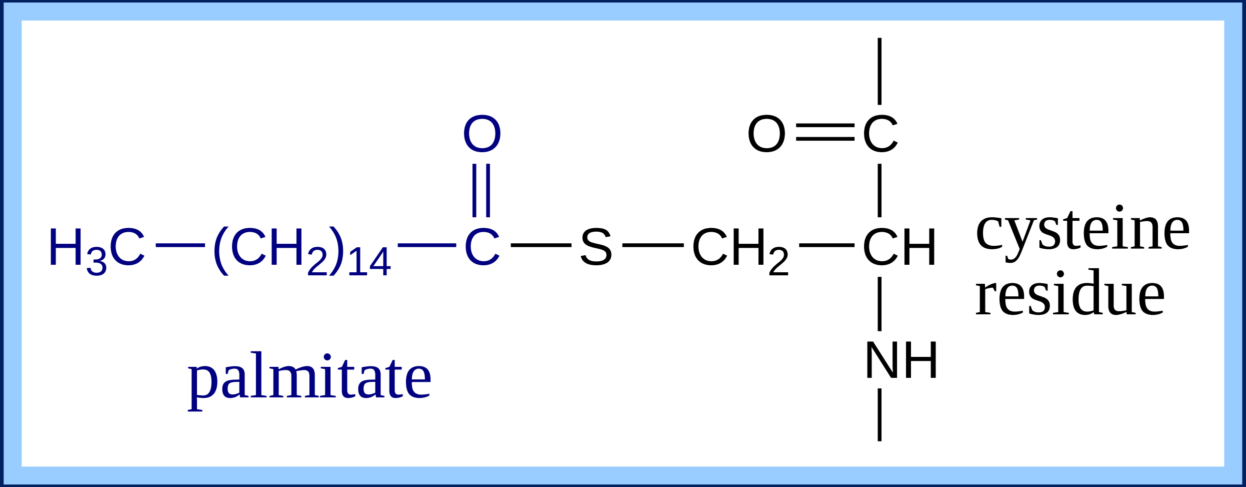


Peripheral proteins are on the membrane **surface**.

They are water-soluble, with mostly hydrophilic surfaces.

Often peripheral proteins can be dislodged by conditions that disrupt **ionic & H-bond interactions**, e.g., extraction with solutions containing high concentrations of salts, change of pH, and/or chelators that bind divalent cations.

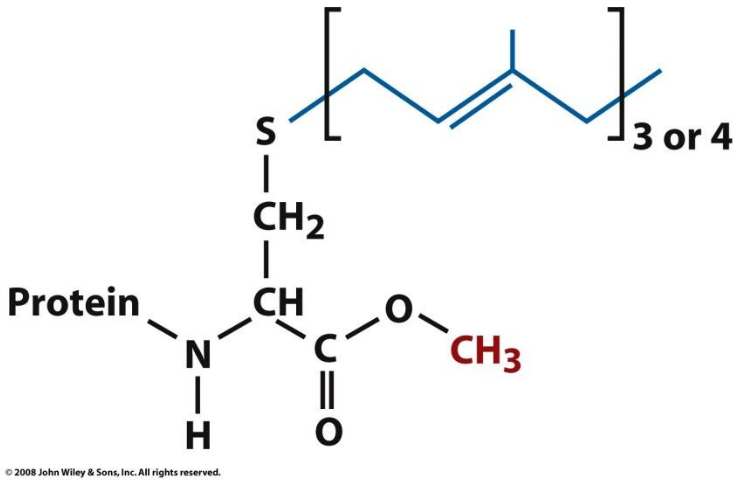




A protein may link to the cytosolic surface of the plasma membrane via a covalently attached **fatty acid** (e.g., palmitate or myristate) **or**
an isoprenoid group.

Palmitate is usually attached via an *ester linkage* to the thiol of a cysteine residue.

A protein may be released from plasma membrane to cytosol via depalmitoylation, hydrolysis of the ester link.



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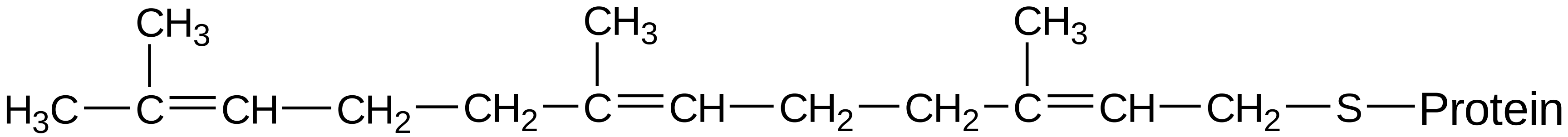
Prenylated Proteins

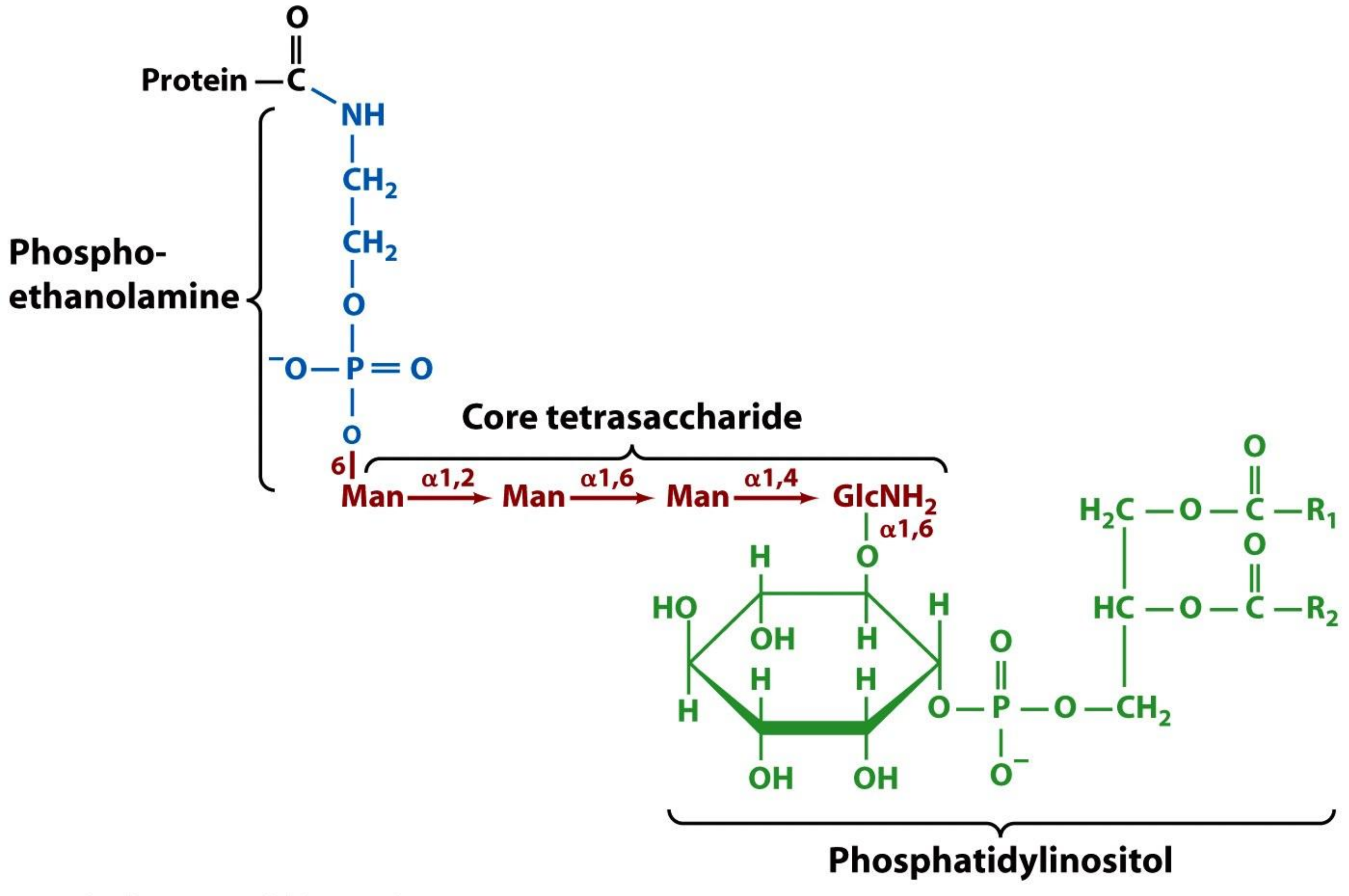


$$H_3C-\overset{CH_3}{\overset{|}{C}}=CH-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}}=CH-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}}=CH-CH_2-S-\text{Protein}$$

farnesyl residue linked to protein via cysteine S

An **isoprenoid** such as a **farnesyl** residue, is attached to some proteins via a thioether linkage to a cysteine thiol.

Core Structure of the GPI Anchors of Proteins



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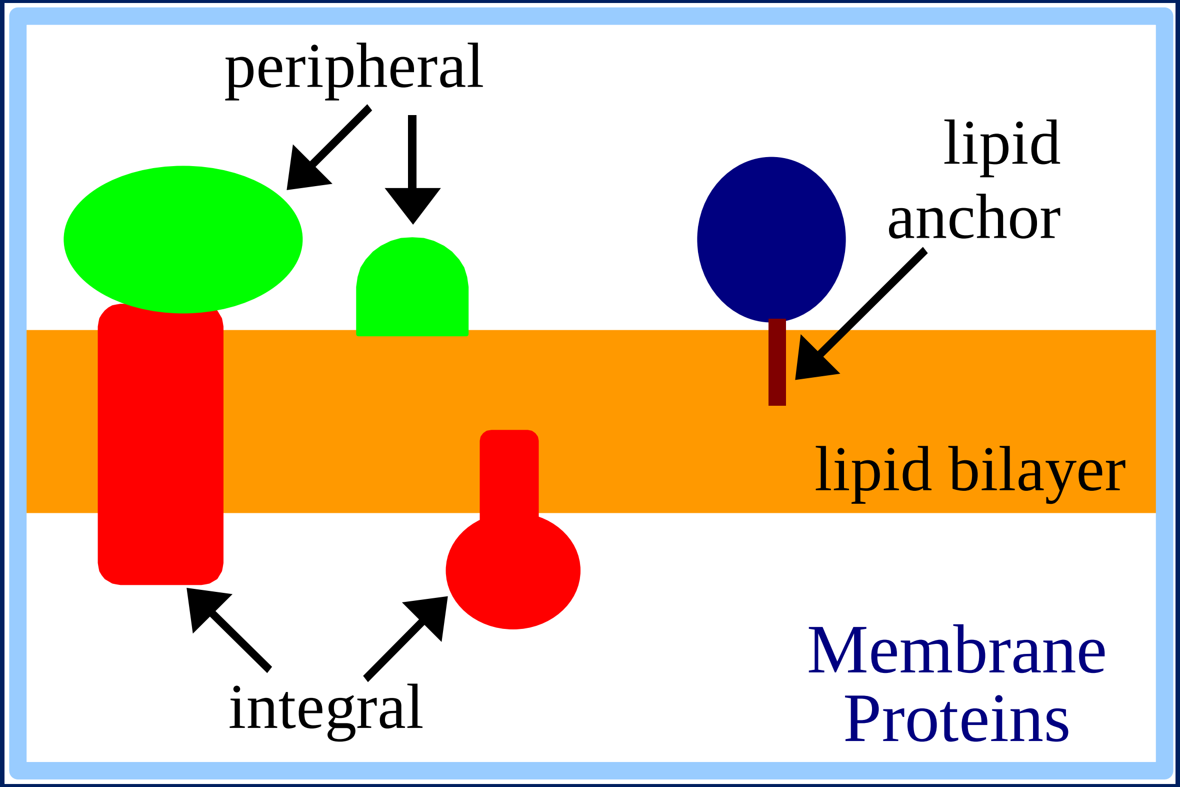
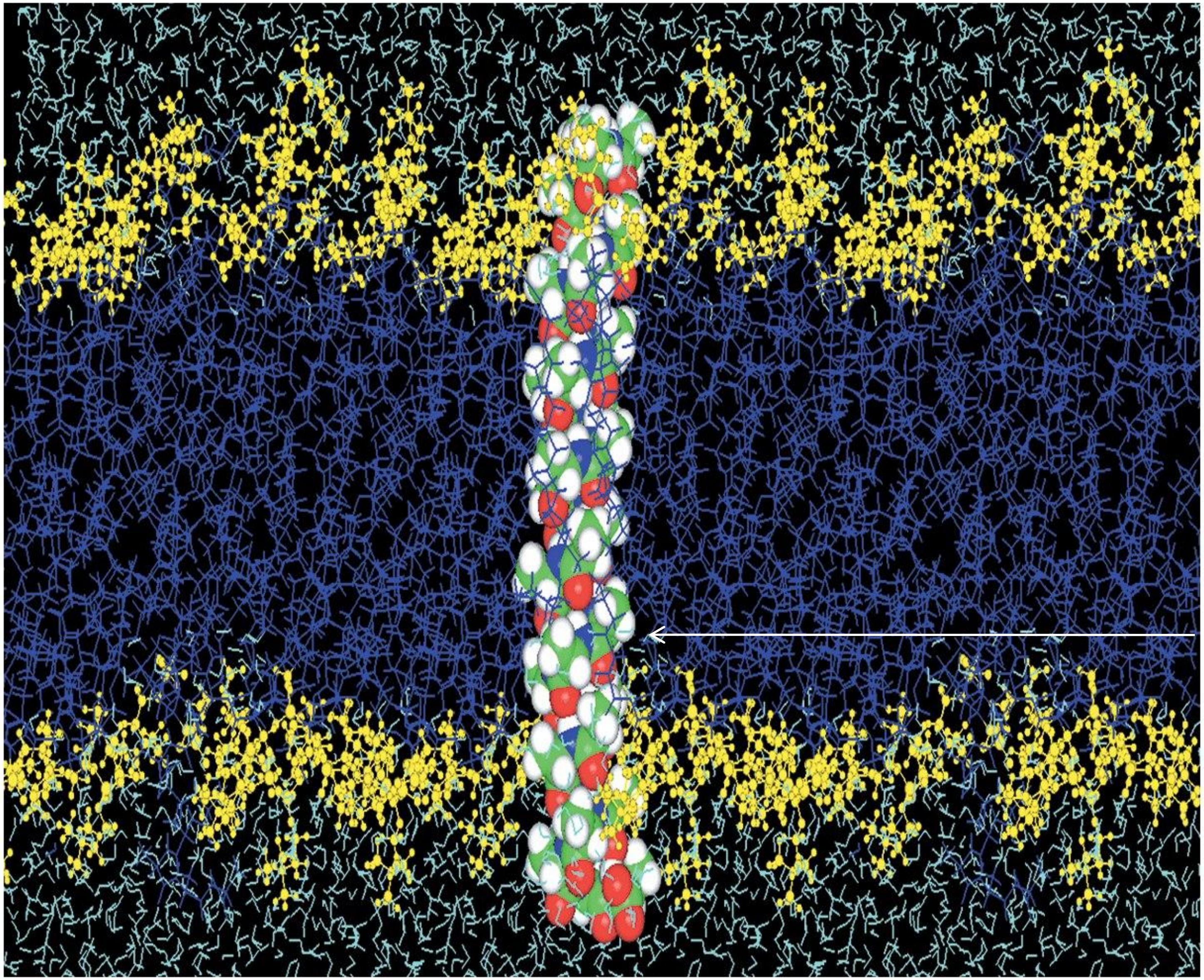


Integral proteins have domains that extend into the hydrocarbon core of the membrane.

Often they span the bilayer.

Intramembrane domains have largely **hydrophobic surfaces**, that interact with membrane lipids.



Chapter 4 Opener Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

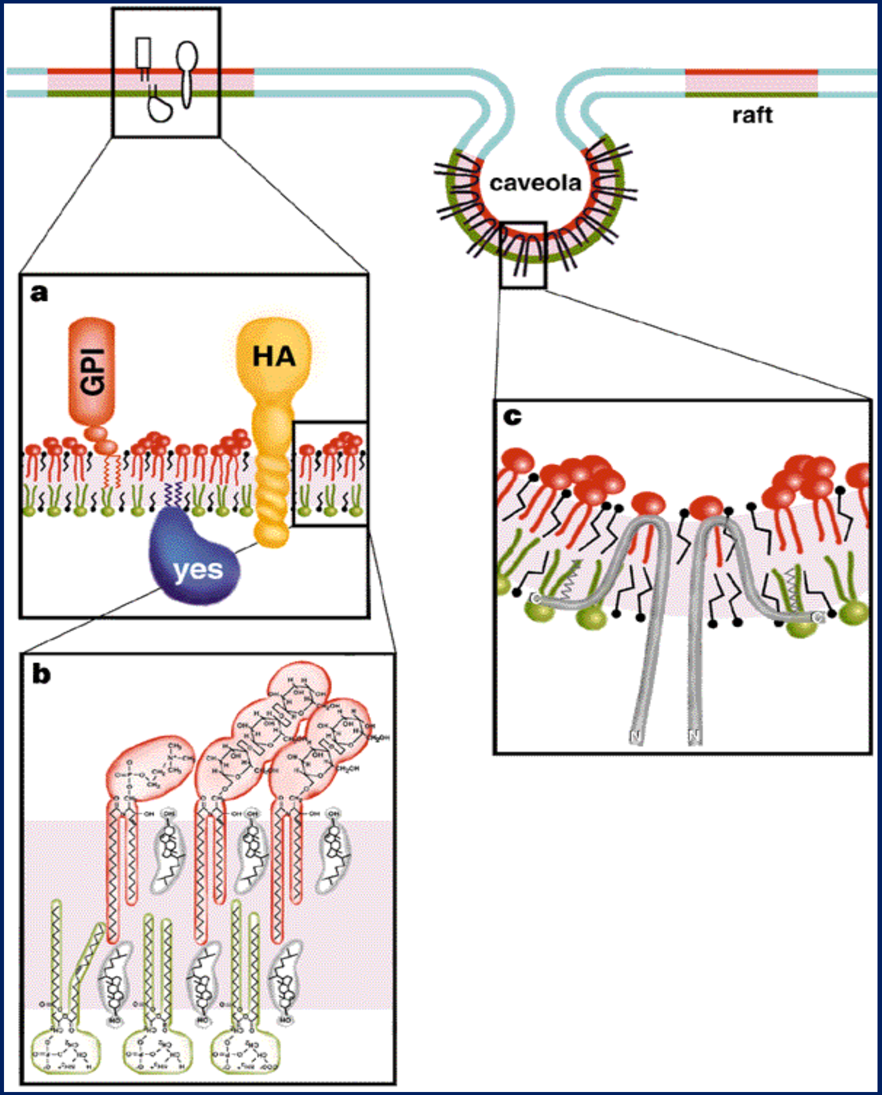
Fatty acid chains

Transmembrane protein

Polar head groups

Simulation of a fully hydrated, fluid bilayer composed of Phosphatidylcholine
Penetrated by a single transmembrane helix.

Lipid rafts



- Membrane microdomains enriched in glycolipids and cholesterol
- Function by segregation: some proteins are enriched in rafts, others are excluded
- Participate in TGN-to-PM trafficking of apically-destined proteins
- Function at the PM in endocytosis and in organizing cell signaling pathways
- Controversial model

Simons and Ikonen (1997) Nature 387:569

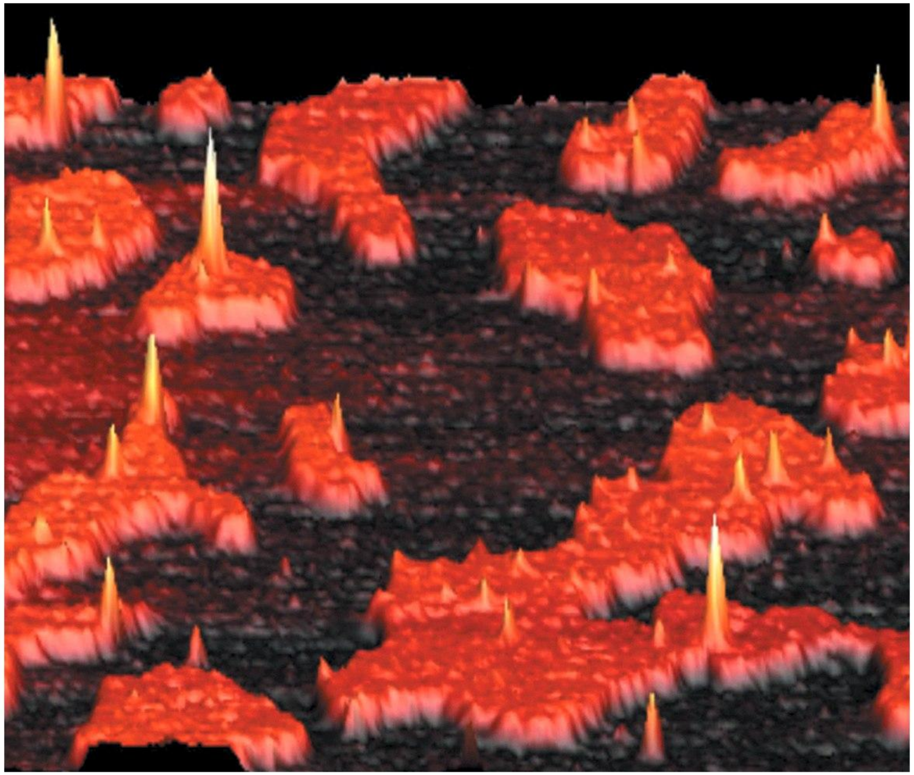


Figure 4-23a Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

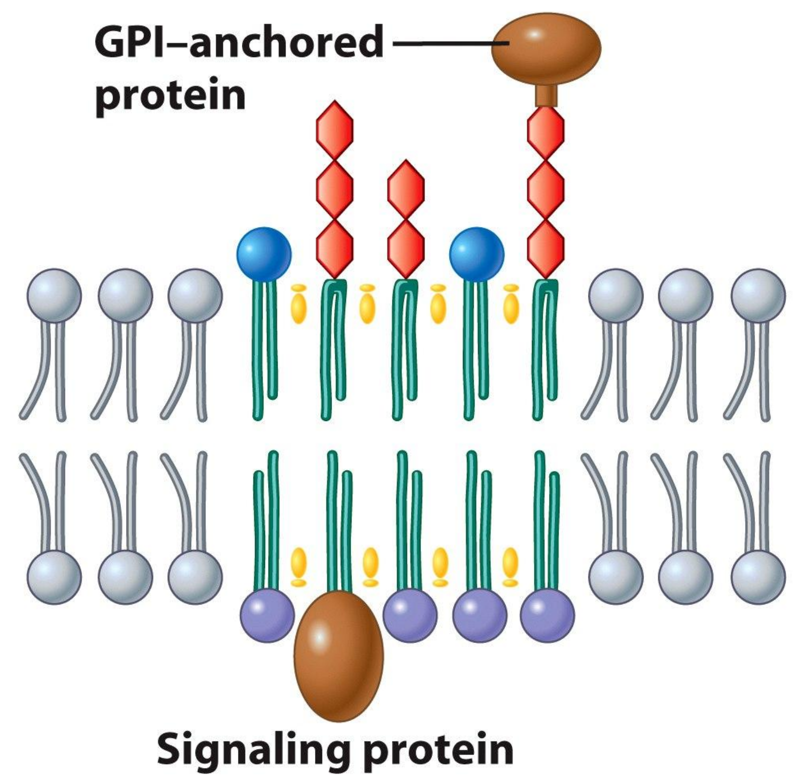


Figure 4-23b Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Lipid Rafts – Left side artificial membrane with rafts and right side is a schematic model of a lipid raft within a cells.

Proteins involved in cell signaling often associate with lipid raft domains

The "linear" pathway from arachidonate to leukotrienes

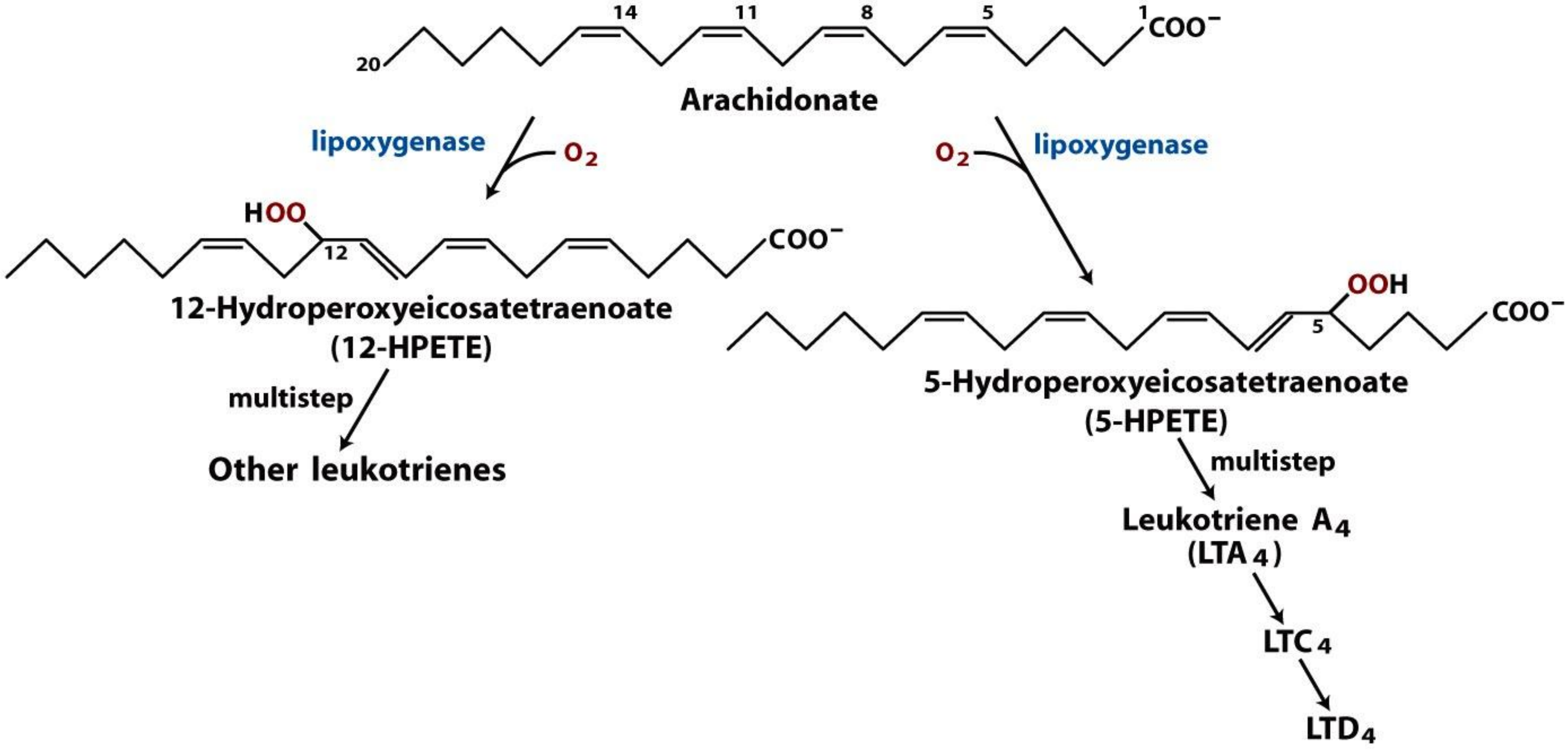
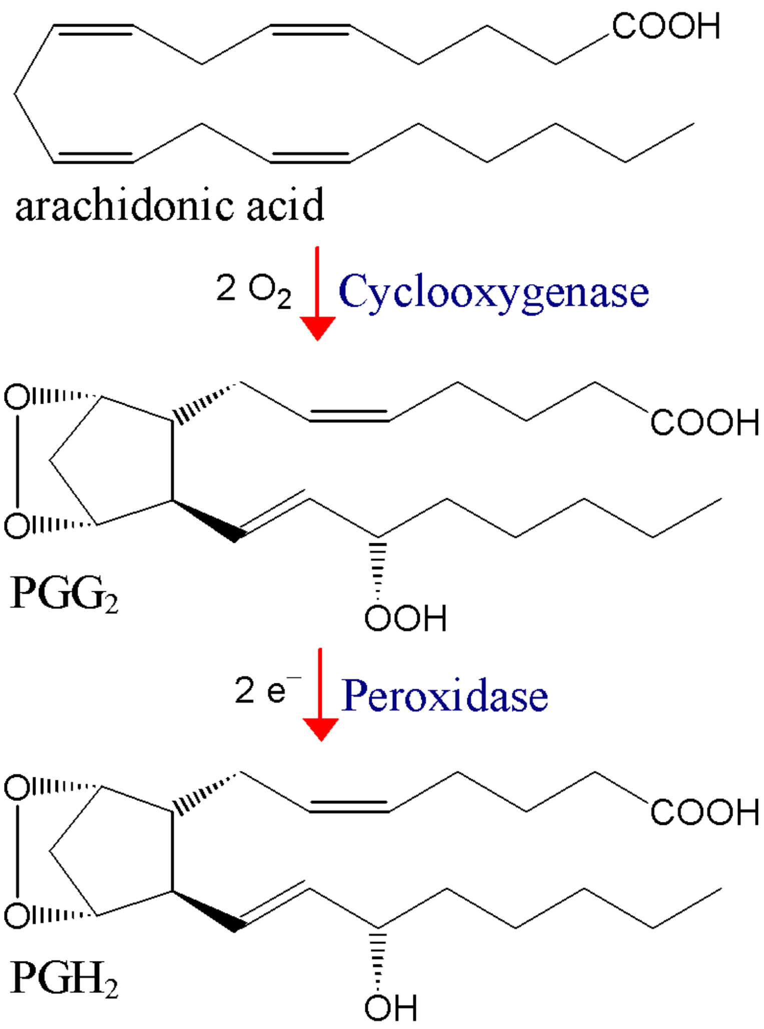


Figure 21-16
Lehninger Principles of Biochemistry, Fifth Edition
© 2008 W. H. Freeman and Company

"Cyclic" synthesis from arachidonate to prostaglandins

- The free arachidonic acid is oxidized and cyclized in the ER by endoperoxide synthase (PGH_2 synthase)
- This enzyme has two activities – cyclooxygenase (COX) and peroxidase
- Initially yields PGH_2
- Subsequent steps lead to thromboxane A_2 and various prostaglandins



Синтез азот-содержащих органических соединений

- Синтез аминокислот
- Синтез гликопротеинов и протеогликанов (на экспорт)
- Синтез нуклеозидов и НК
- Синтез коферментов
- Синтез и фолдинг белков в цитозоле

Biosynthesis of Amino Acids

цитозоль

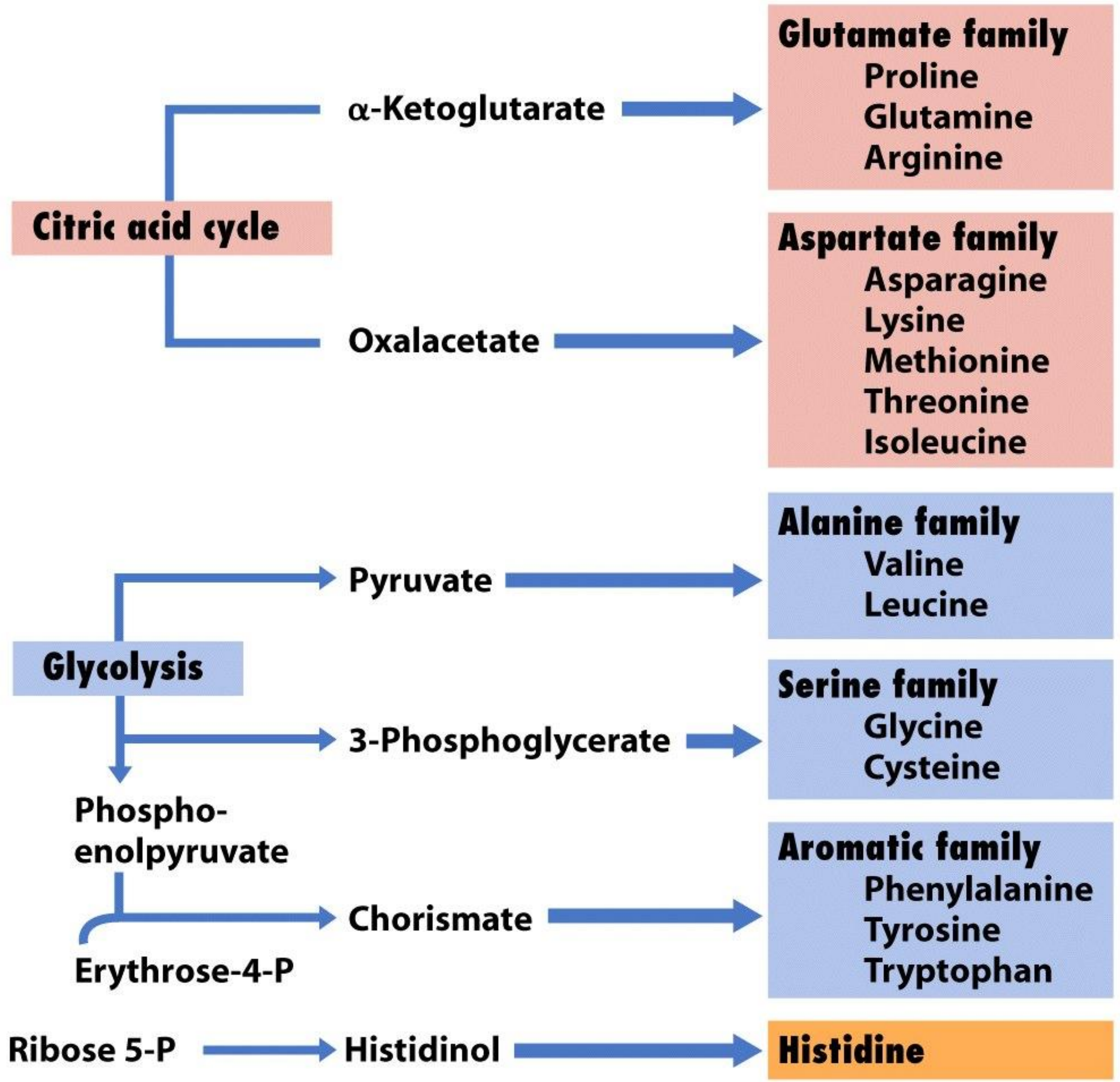


Figure 5-26 Brock Biology of Microorganisms 11/e

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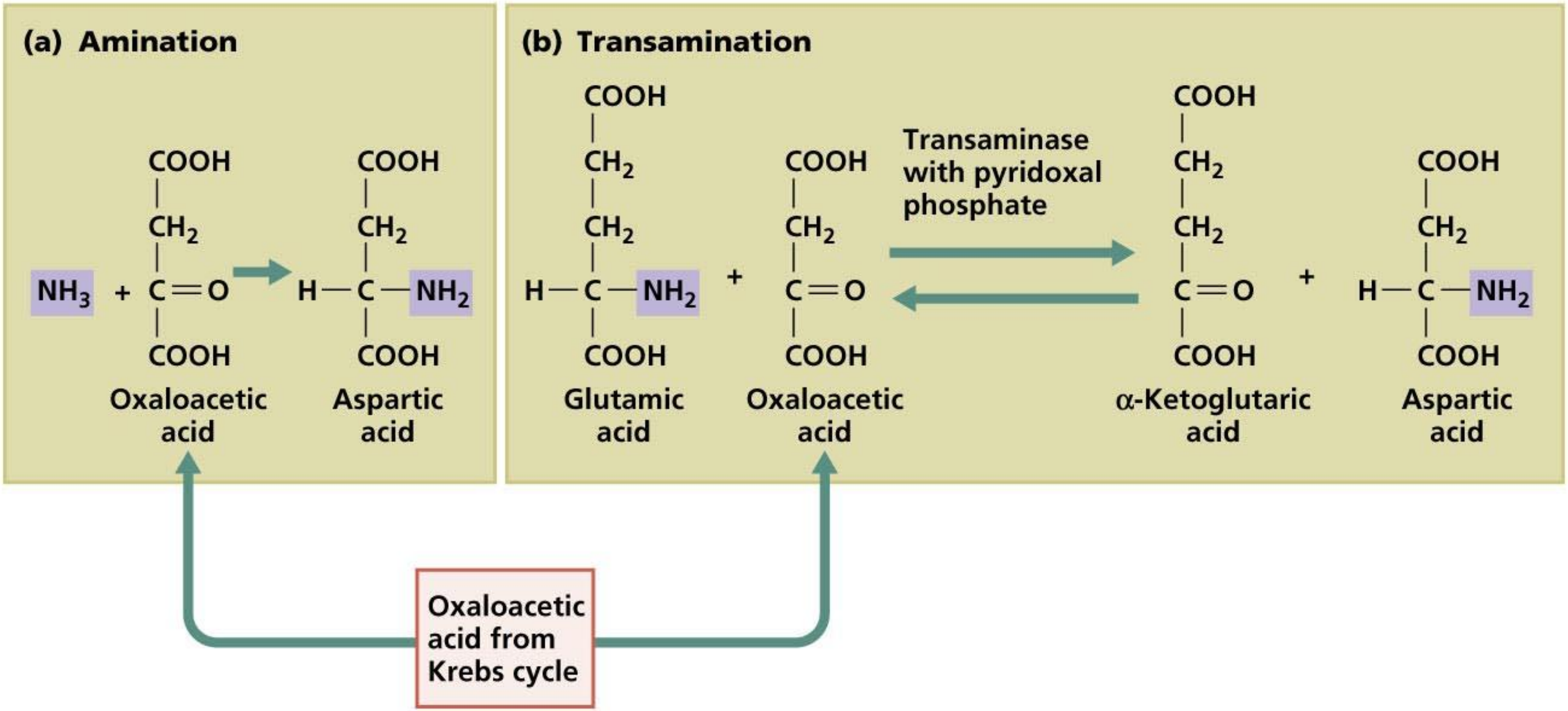
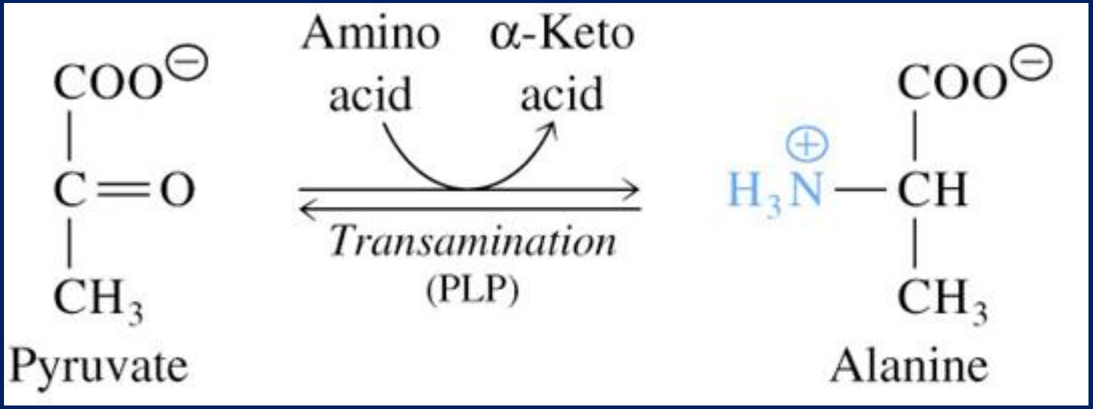
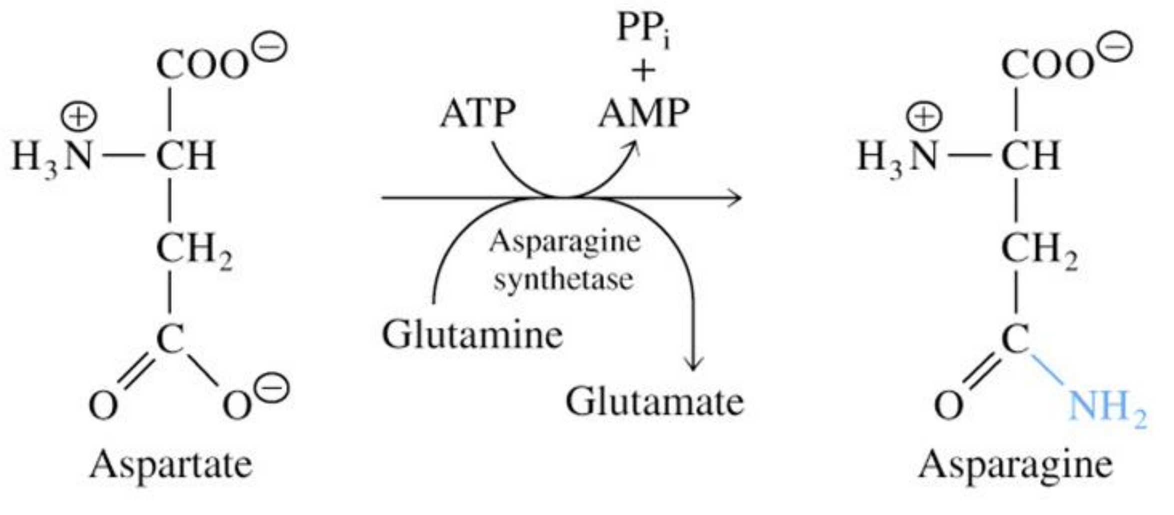
Anabolic Pathways – Amino Acid Biosynthesis



Transamination



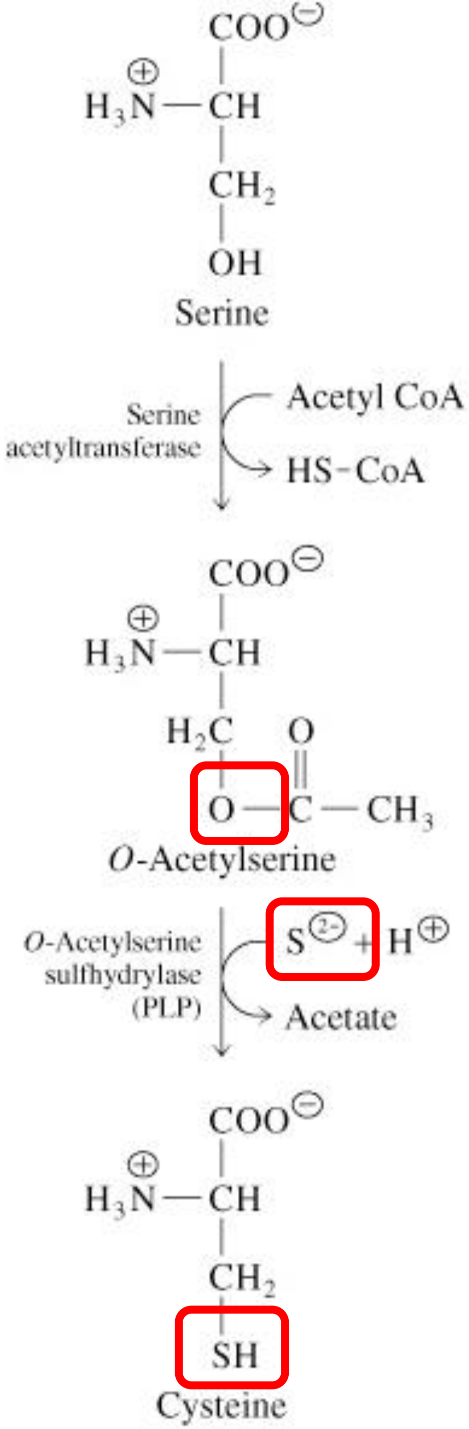
Amides synthesis



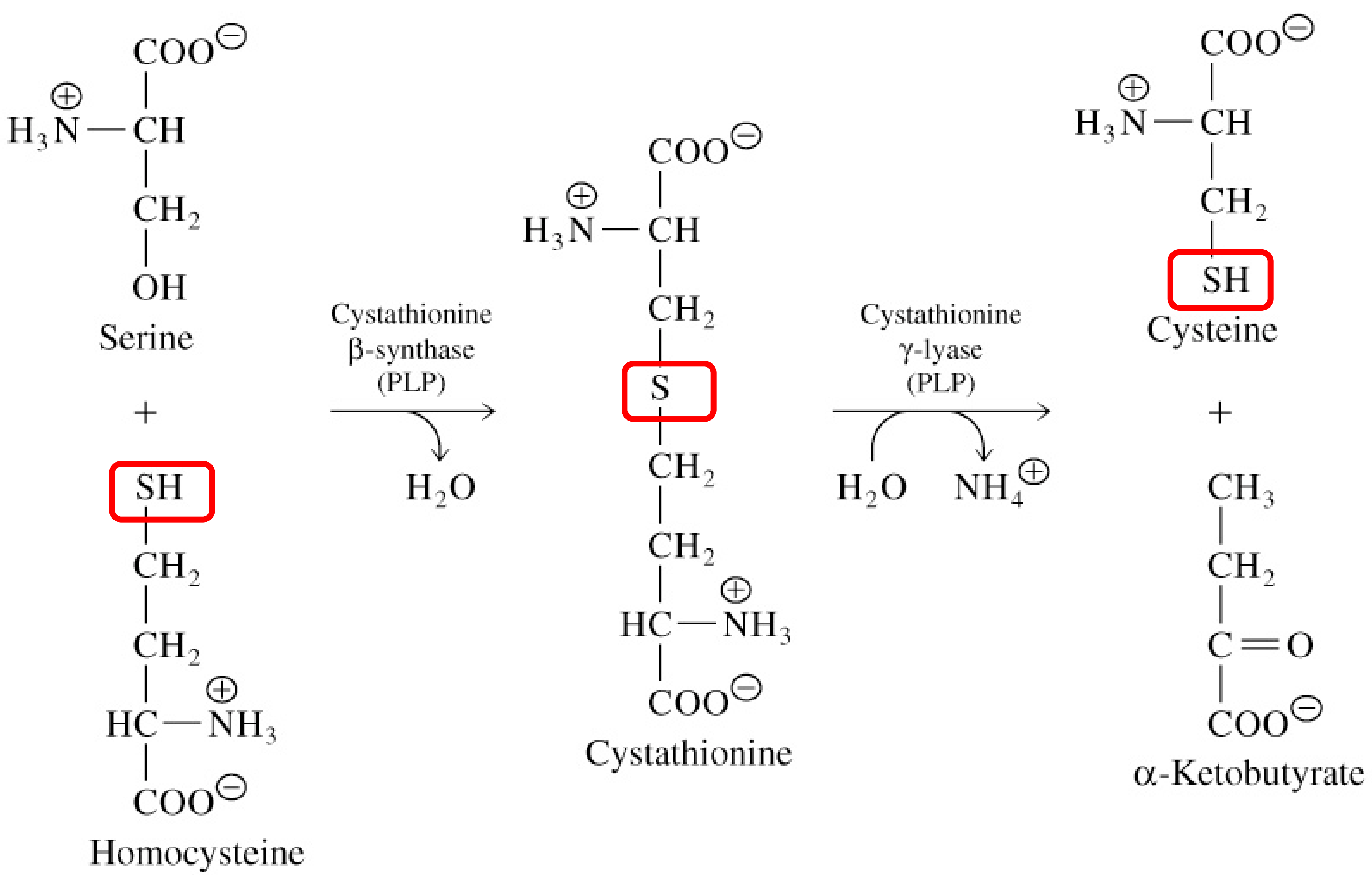
Предшественник →	Аминокислоты - продукты
Пируват	1) Аланин 2) Валин 3) Лейцин
Оксалоацетат	1) Аспартат+ Аспарагин 2) Лизин 3) через гомосерин → метионин и треонин 4) Из треонина →изолейцин
Альфа-оксоглутарат	1) Глутамат+ глутамин 2) Аргинин 3) Пролин
3-фосфоглицерат	Серин, глицин, цистеин
ФЕП+ Эритрозо-4-фосфат	Фенилаланин, тирозин, триптофан
5 фосфорибозил-пирофосфат+АТФ	гистидин

Cysteine biosynthesis from Ser *in bacteria and plants*:

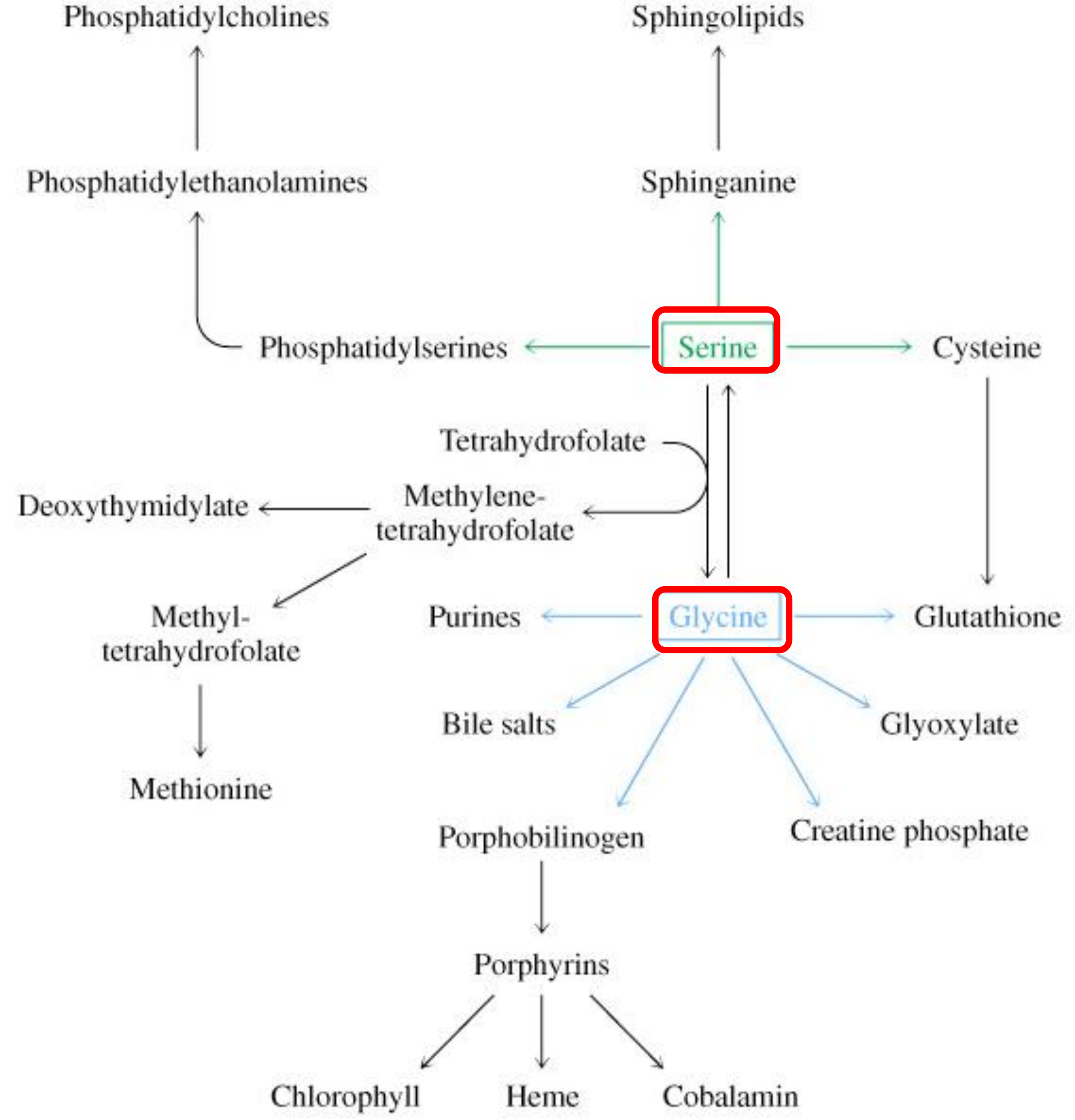
- Serine acetyltransferase
- Acetylserine sulfhydrolase



Cysteine biosynthesis *in mammals*

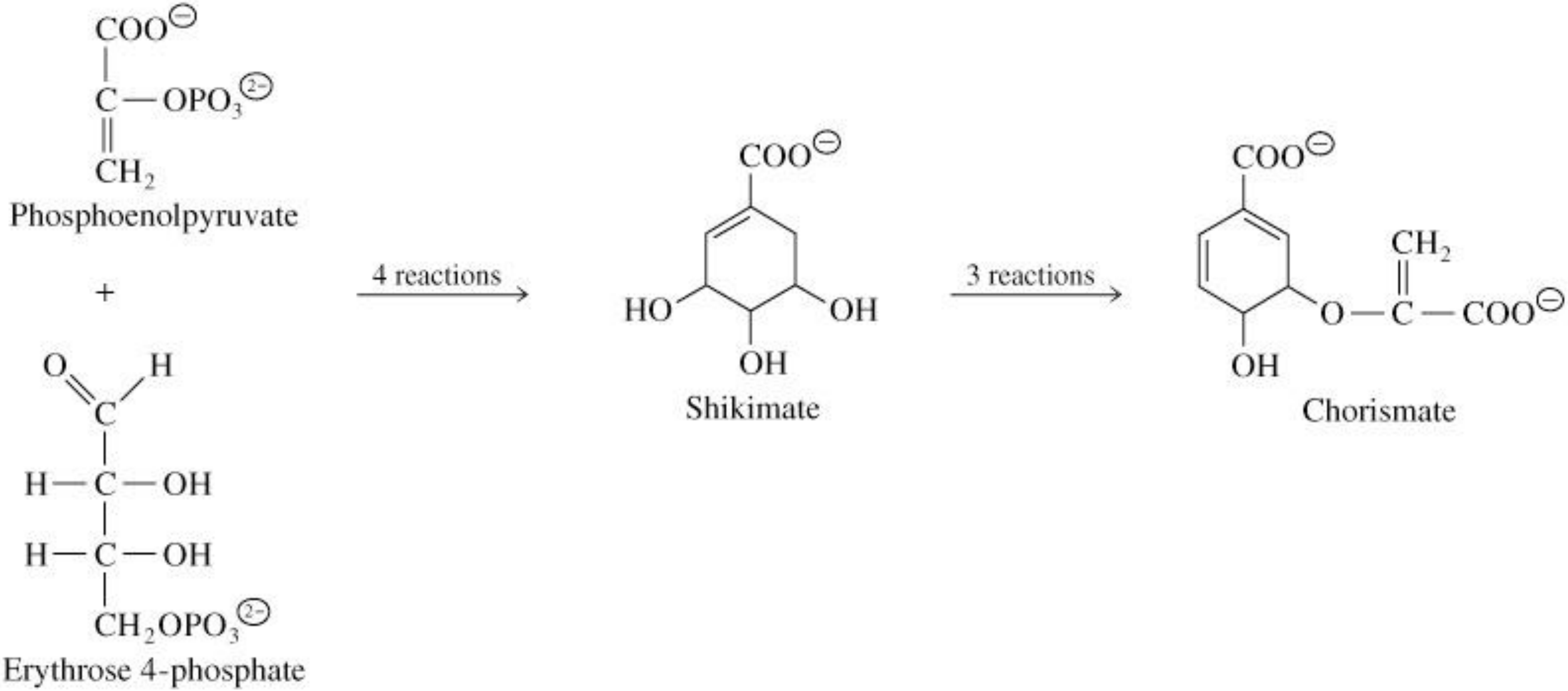


- Compounds formed from serine and glycine

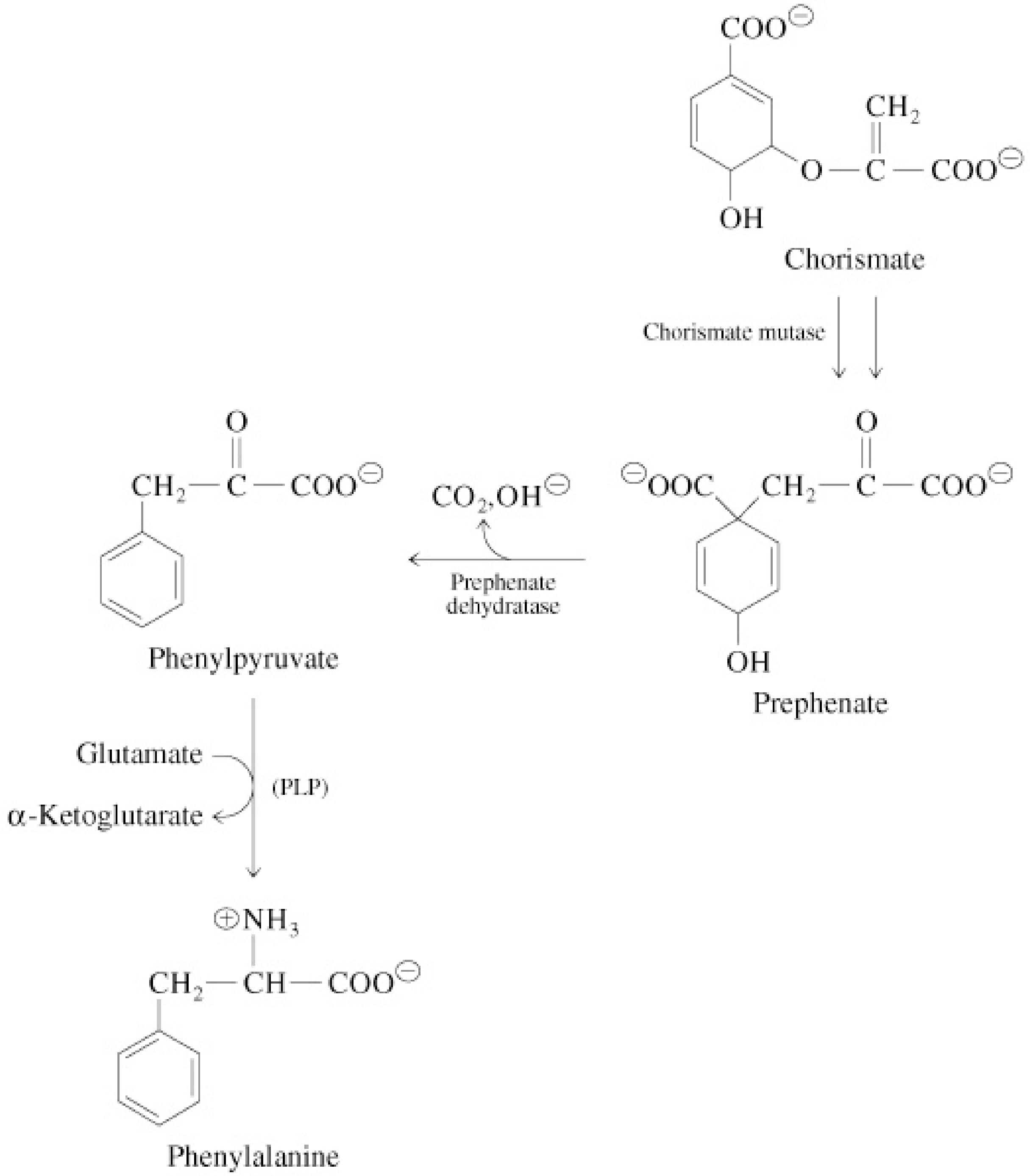


The Aromatic Amino Acids

- Shikimate and chorismate are key intermediates



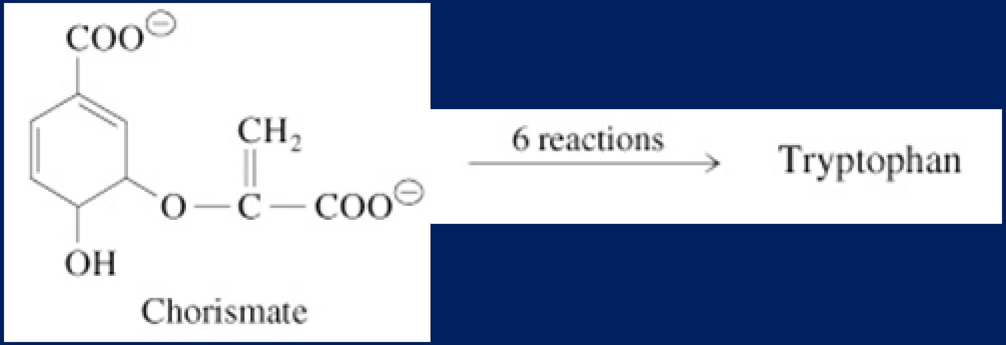
Biosynthesis of Phe and Tyr from chorismate

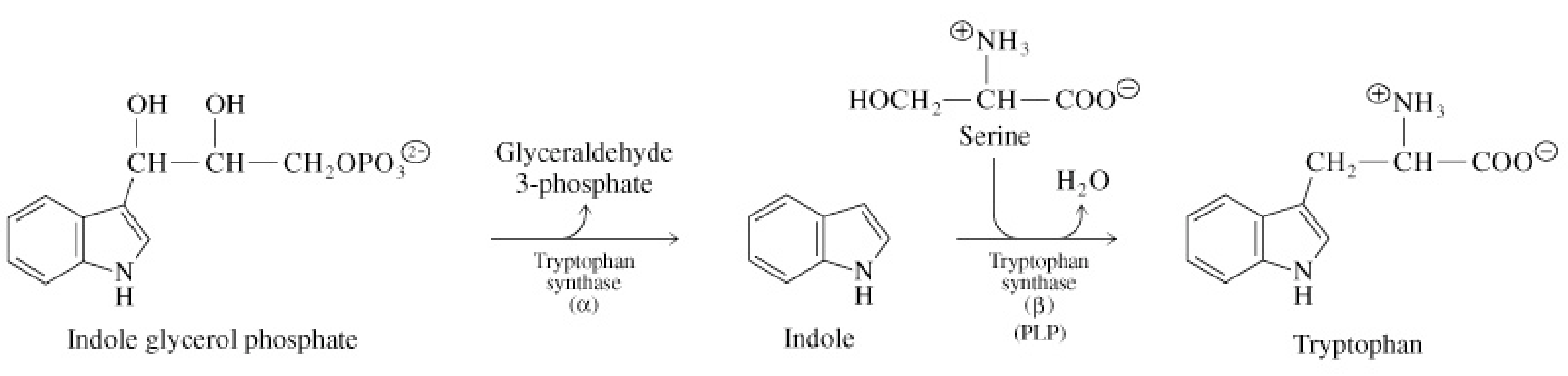


(Tryptophan biosynthesis)

(Tyrosine biosynthesis)

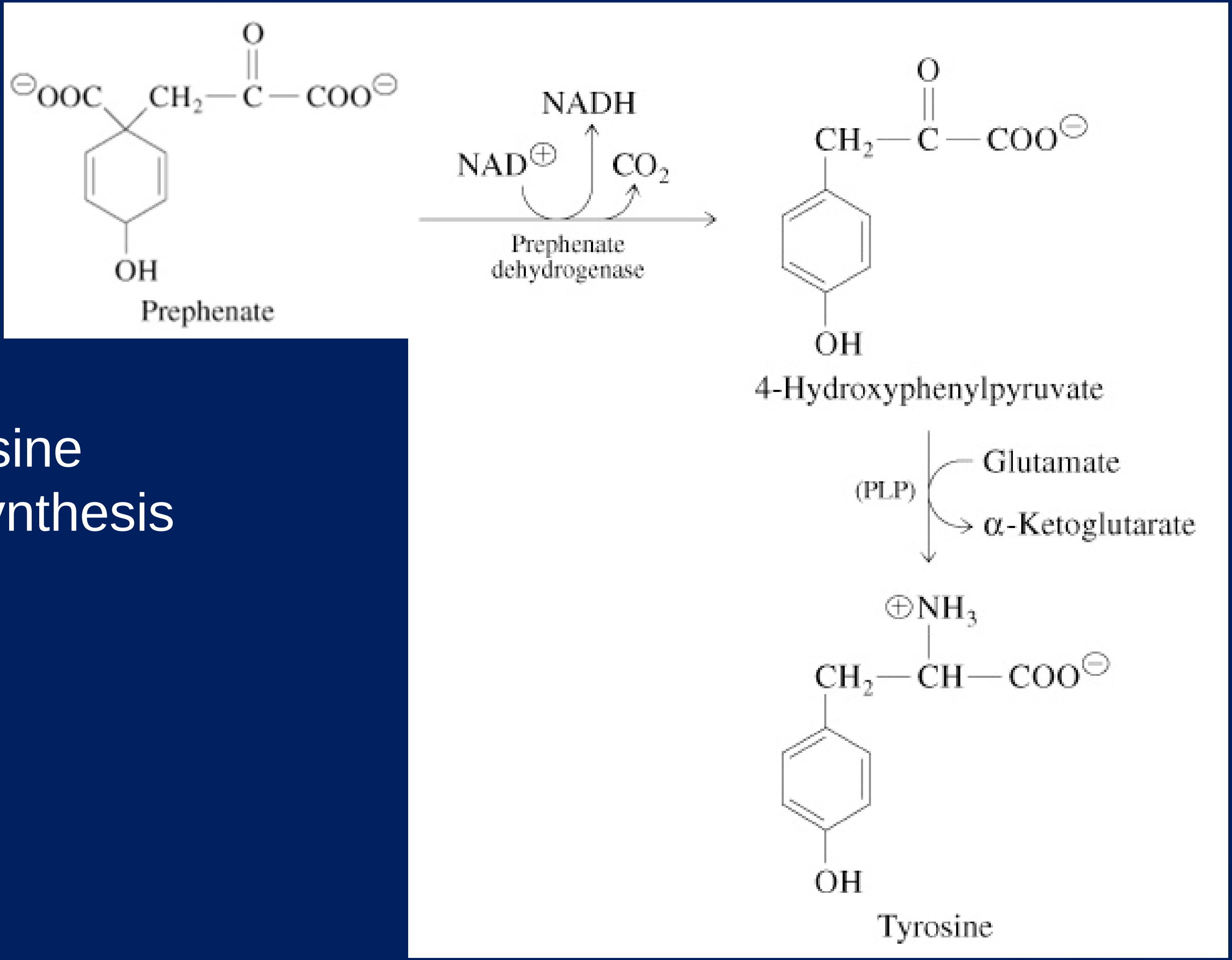
Tryptophan biosynthesis (last 2 steps)



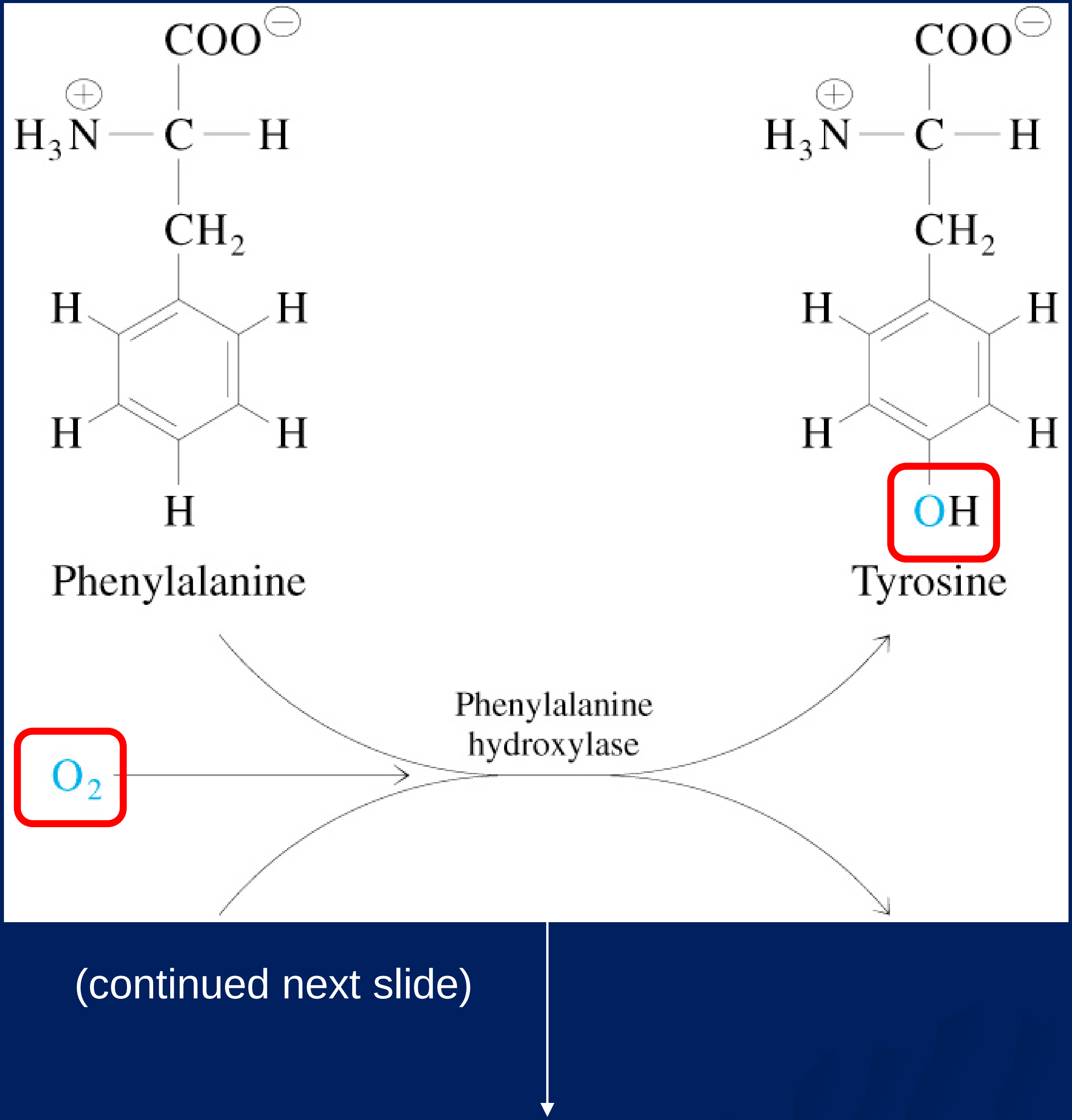


(last 2 steps)

Tyrosine biosynthesis

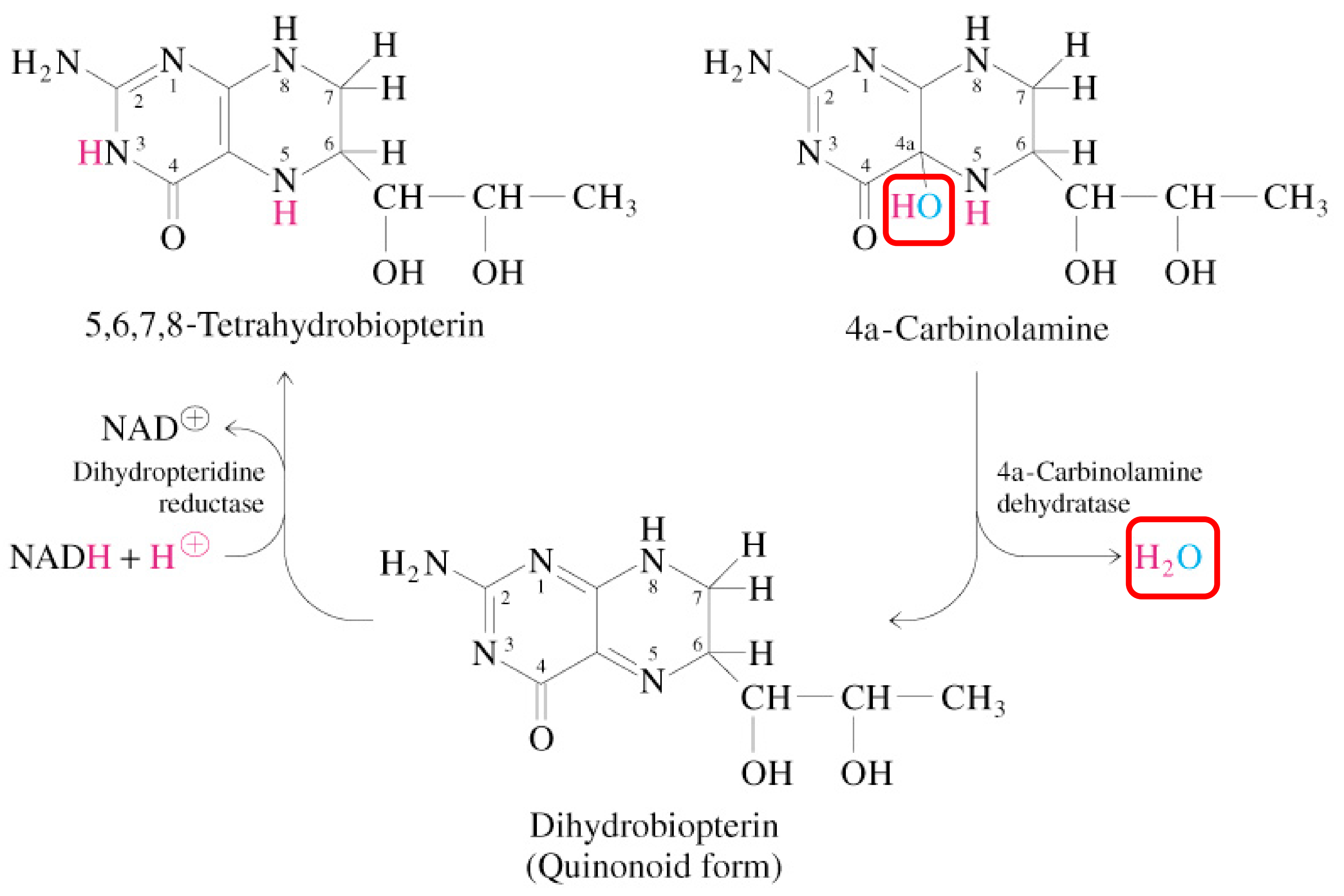


Tyrosine synthesis from Phe

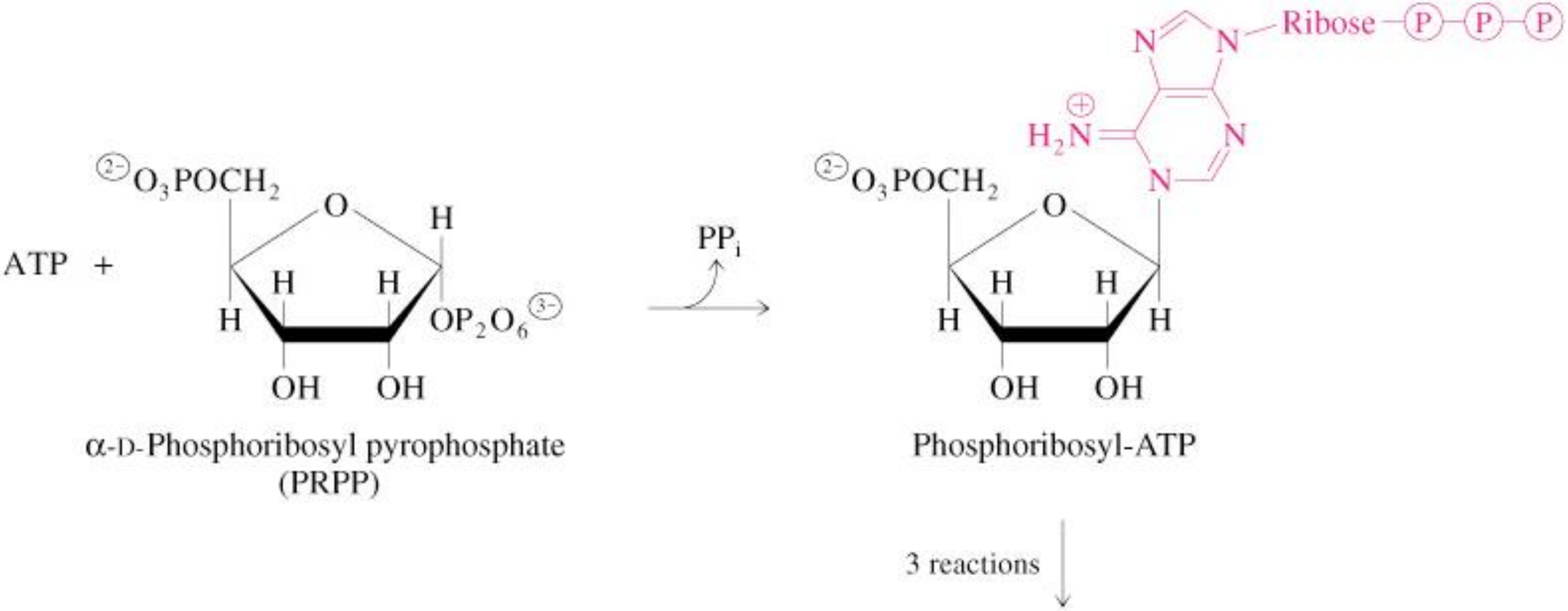


(continued next slide)

(continued to Tyr)


5,6,7,8-Tetrahydrobiopterin
4a-Carbinolamine
HO
4a-Carbinolamine dehydratase
H_2O
Dihydrobiopterin (Quinonoid form)
Dihydropteridine reductase
$NAD^{\oplus}$
$NADH + H^{\oplus}$

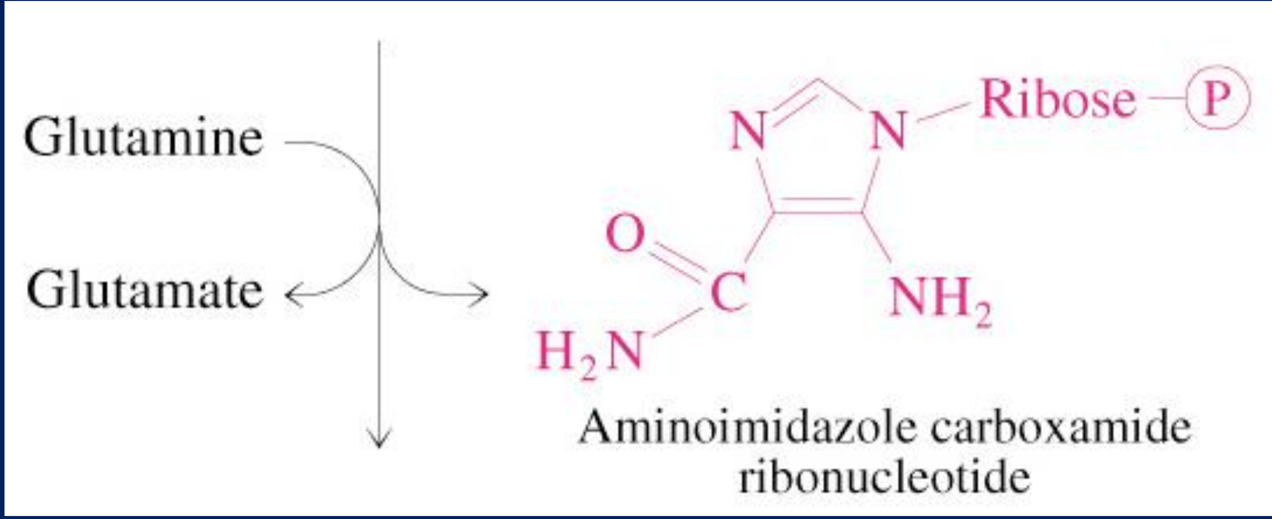
6) Histidine



α-D-Phosphoribosyl pyrophosphate (PRPP)

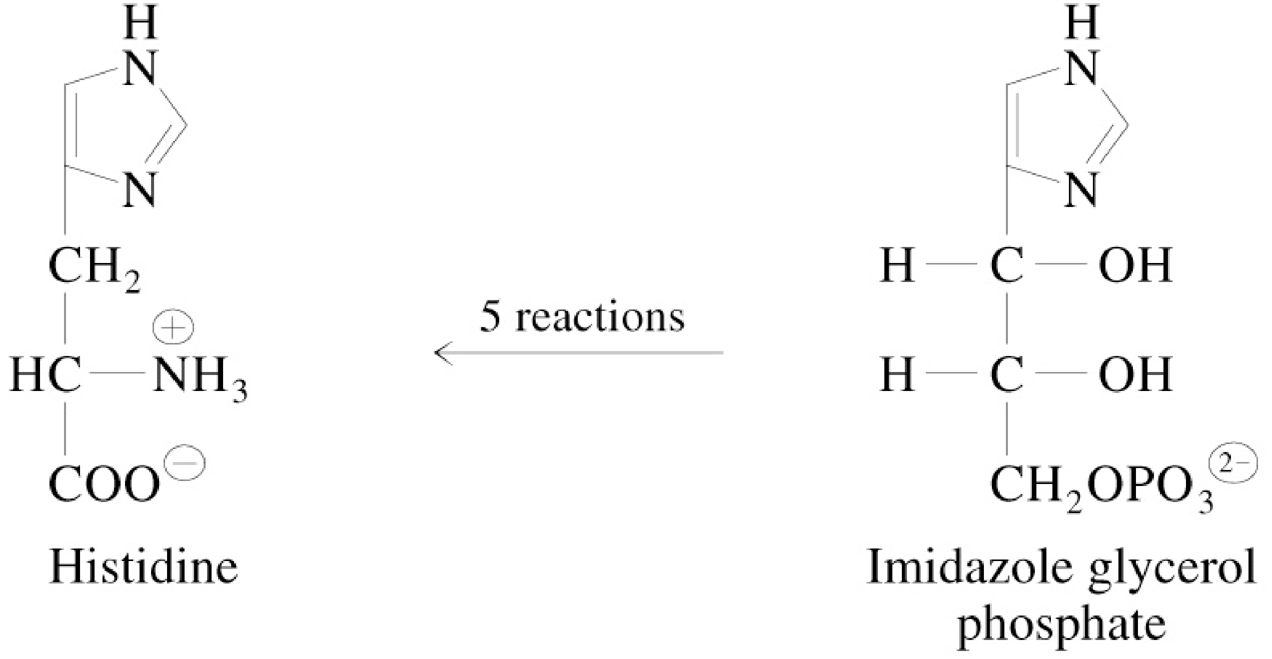
Phosphoribosyl-ATP

(next slide)



Aminoimidazole carboxamide ribonucleotide

purines



Histidine

Imidazole glycerol phosphate